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BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 12 1952

CONCERNING THE MECHANISM OF ANAPHYLAXIS AND ALLERGY

BY

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The abnormal reaction of tissues to apparently harmless agents, such as foreign sera, egg albumen, house dust, animal dander, foods, cosmetics, drugs, etc., that is called anaphylactic or allergic is as yet not well understood. For fifty years physiologists, immunologists, pharmacologists, and clinicians have endeavoured to solve the riddle of how and why, after repeated contact with such an agent, the organism becomes sensitized to it in such a way that reaction to its renewed contact may result in death.

The phenomenon of anaphylaxis was first described by Portier and Richet (1902) on the basis of experiments performed in a dog receiving two small doses of an extract of sea actinia. The tentacles of this coelenterate were extracted with glycerin and the lethal dose in dogs was estimated. When the dog that had survived an injection of 1/50 of the lethal dose received a second injection a few days later an extremely severe picture of acute intoxication developed and the animal died in a few minutes. It did not appear to have become immunized; on the contrary, it became hypersensitive, apparently by losing its natural immunity to the venom. The name "anaphylaxis" was given by Portier and Richet (1902) to indicate this first theoretical explanation of the phenomenon. Similar phenomena were described by Arthus (1903) in the rabbit and by Otto (1907) in the guinea-pig, by using horse serum as the agent to elicit anaphylactic shock.

Theories to Explain Anaphylaxis

The number of different and independent theories formulated to explain the phenomenon of abnormal sensitivity to such agents already indicates the complexity of the mechanism underlying anaphylaxis. The first explanation proposed by Richet was only a translation of the observed phenomena into other words. According to him, the actino-congestin generates a "toxogenin," which would react with the congestin (the sea anemone extract) to generate the "apotoxin." This explanation, however, can be changed to conform to the views of the immunologists by substituting the term "antigen" for actino-congestin, "antibody" for toxogenin, and "antigen-antibody complex" for apotoxin, with the difference that this complex is not a toxin but releases a complicated process in the tissues, leading to a discharge of the toxic agents. Also, as simply verbal explanations might be listed a number of theories that ascribe the mechanism of anaphylaxis to physical changes in the colloidal equilibrium of the blood, alterations of the cell membrane, and so forth.

Nolf (1910) assumed that the anaphylactic reaction would depend upon the release of a thromboplastic agent that would produce local coagulation of the blood with the deposit of a fibrin network upon the endothelial cells, resulting in an increased capillary permeability, with the formation of oedema and also of microthrombi. We might describe Nolf's theory as semi-verbal, since it already contained a few points that might inspire an experimentally sound approach to the problem.

The first attempt to build up a reasonable theory of anaphylaxis was made by the German workers Friedberger (1909) and Friedeman (1909), and, later, the idea was developed by the Belgian immunologist J. Bordet (1913). When the specific precipitate obtained by mixing the antibody (serum of immunized rabbit) with the antigen (horse serum) is washed and incubated with guinea-pig serum, it generates an agent that produces a severe or lethal shock when injected intravenously into a guinea-pig. The substance generated in the serum by incubation with the specific precipitate was called "anaphylatoxin" or "serotoxin." Keysser and Wassermann (1911), Bordet (1913), and Nathan (1913) have shown that other substances, such as kaolin, barium sulphate, agar, and inulin, might be employed in the place of the specific precipitate to produce the anaphylatoxin. The idea that a blood-borne toxin (serotoxin) would explain the genesis of anaphylactic shock was the basis for the so-called "humoral theory" of anaphylaxis.

About the same time, Dale (1913) developed the theory that the phenomenon of smooth-muscle contraction and increased capillary permeability that is peculiar to anaphylactic shock was a consequence of the reaction of the antigen with the antibody anchored to the tissues. On the basis of the profound analogy between the effects of histamine and those of anaphylaxis, Dale (1920) postulated the theory that this substance might be either released or produced as a consequence of the combination of the antigen with the antibody at the level of the cell surface. Since the anaphylactic smooth-muscle contraction could be produced *in vitro* by simply adding the antigen to the bath containing a piece of sensitized guinea-pig uterus, without any participation of the blood, Dale's conception of the mechanism of anaphylaxis became known as the "cellular theory" of anaphylaxis.

The two theories—the "humoral" and the "cellular"—have always been regarded as highly conflicting or strongly opposed views, and therefore they could not possibly coexist as explanations for the same phenomenon. This dramatic situation was closely analysed by Dale and Kellaway (1922). Since the so-called anaphylatoxin could not affect the smooth musculature of the guinea-pig uterus or gut suspended in a bath, it could not be the culprit of the anaphylactic phenomenon. In the pithed guinea-pig

submitted to artificial respiration a ligature on the aorta and vena cava at the level of the diaphragm did not stop the immobilizing effect of the agar-anaphylatoxin upon the movements of the lungs induced by artificial respiration. Dale and Kellaway (1922) state: "We are left practically with the lungs themselves, their blood vessels, the blood circulating through them, and the heart which propels it. In this limited mechanism all that anaphylatoxin can affect is the bronchial obstruction. On the plain muscle isolated from the body they have no action adequate to account for it . . . there remain the blood and the endothelium of the blood vessels." If the lungs were perfused without any blood it would be found that anaphylatoxin immobilizes them as well, since it works by liberating histamine, as demonstrated recently in our laboratory (Rocha e Silva, Aronson, and Bier, 1951).

However, the arguments presented by Dale and Kellaway were so convincing, and the further demonstration of the liberation of histamine by the direct contact of the antigen with the washed organs of the sensitized guinea-pig so clearly demonstrated, that the studies on the mechanism of formation and the mode of action of anaphylatoxins have remained practically at a standstill for the past 20 years.

Liberation of Histamine in Anaphylactic Shock

The first clear-cut demonstration of a discharge of histamine during anaphylactic shock was made by Bartosch, Feldberg, and Nagel (1932) by perfusing the lung of the sensitized guinea-pig with the antigen. The amounts of histamine released under such conditions were, however, very small. Only 0.4 to 4 μg. of histamine was released by long-continued perfusion with horse serum. These findings were confirmed by Daly, Peat, and Schild (1935) by perfusing the guinea-pig lung, with horse serum and egg albumen as antigens. Although the histamine outputs were even smaller when horse serum was used, the histamine discharge by egg white was in one case as high as 12.8 μg.; the usual total discharge was only a few micrograms. Since the blood was not a part of the perfusion system, the "cellular theory" received important support from those experiments and from other experiments with the isolated pieces of organs of guinea-pigs (Ungar and Parrot, 1936; Schild, 1939; Emmelin, Kahlson, and Lindström, 1941).

In the rabbit and the dog, however, the exclusion of the blood constituents from participation in the mechanism of histamine release was not so clear-cut. In the rabbit the demonstration of the release of histamine under the influence of the antigen was made by using a sample of blood to which the antigen was added and estimating the amount of histamine shifting from cells to plasma (Katz, 1940; Dragstedt, De Arellano, Lawton, and Youmans, 1940; Rose and Browne, 1941). Of course, the importance of the blood for the release of histamine in that case might be purely accidental. But in the dog the importance of the blood for the release of histamine in anaphylactic and peptone shock was conclusively demonstrated. It was a known fact that the histamine that appears in the circulating blood in a dog submitted to those kinds of shock derives mainly from the liver. Estimations of liver histamine in fragments of the organ, made before and after shock, indicated the release of milligrams of histamine (Ojers, Holmes, and Dragstedt, 1941; Holmes, Ojers, and Dragstedt, 1941). If, however, the liver is first washed out with Tyrode's solution and then perfused with the shocking agent (peptone or antigen) only small or negligible amounts of histamine will be found in the perfusates, as shown by Rocha e Silva and Graña (1946). If, however, the liver is perfused with total blood kept unclotted in flasks, recovered with silicones, and mixed with peptone or the antigen before being pumped into the organ, enormous quantities of histamine, amounting to milligrams, are released (Rocha e Silva, Scroggie, Fidlar, and Jaques, 1947; Scroggie and Jaques, 1949). As shown in Fig. 1, as much as 8 mg. of histamine

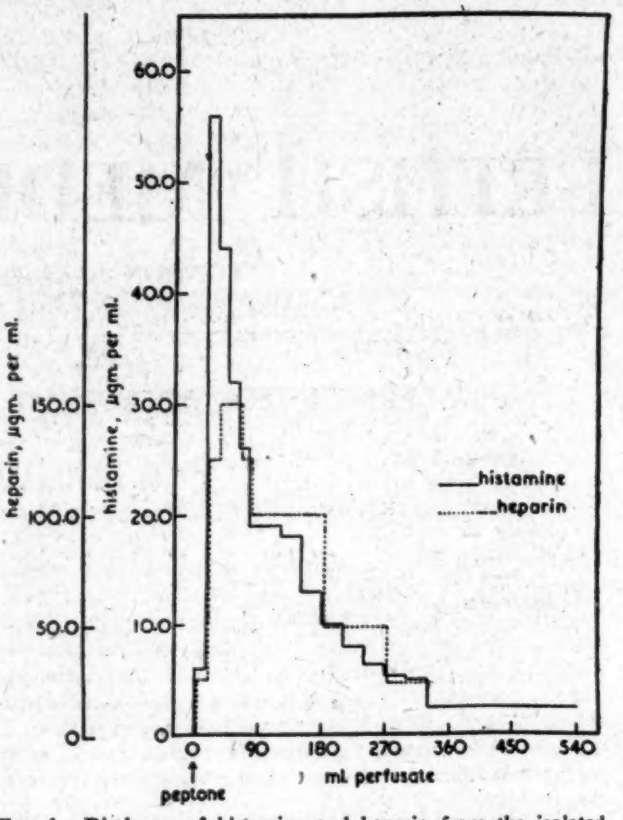

FIG. 1.—Discharge of histamine and heparin from the isolated liver of a dog perfused with peptone in blood kept unclotted in flasks and recovered with silicones (Rocha e Silva, Scroggie, Fidlar, and Jaques, 1947).

and 25 mg. of heparin was released in a few minutes by perfusing the liver with peptone in silicone-recovered blood.

If an anticoagulant such as citrate is added to the blood the estimated amounts of histamine obtained after passage through the liver are not much higher than those obtained with Tyrode's solution. If heparin is used as anticoagulant, a good discharge can sometimes be obtained. In *in vitro* experiments performed by McIntire, Roth, and Richards (1949) a similar inhibition by oxalate and citrate of the histamine release from rabbit blood cells was observed. In agreement with the findings of Dragstedt, Wells, and Rocha e Silva (1942), the inhibition of this shift by adding heparin was only partial.

Microthrombi of Leucocytes and Platelets

The above experiments appeared to indicate the participation of a *blood factor* in the mechanism of histamine release in anaphylactic and peptone shock in the dog and the rabbit. In 1946–7 we presented an analysis of the conditions that might be concerned in the activation of this factor or in the possible nature of it. Most papers on the mechanism of anaphylaxis have concentrated on the study of the histamine release without taking into consideration the other aspects of the problem. At the same time as histamine and heparin are released from the liver of the dog, a sharp fall of the white blood elements takes place, and enormous clumps of leucocytes and platelets are formed almost instantaneously and then suddenly begin to disintegrate. After a few minutes one can find only traces of the previously existing aggregates, and this disintegration is to some extent correlated to the intensity of the discharge of histamine and heparin from the liver cells. Also, an activation of the so-called plasma protease (plasmin or fibrinolysin) takes place, and it appeared to us of interest to try to correlate all these events in a single scheme. On the basis of experiments performed in the dog I assumed (Rocha e Silva, 1950) that the root of the whole mechanism lead-

ing to the histamine discharge was the disintegration of these microthrombi of leucocytes and platelets. The anticoagulants that are known to protect platelets had a definite inhibitory effect upon the discharge of histamine and heparin. In this connexion, citrate was the more powerful and heparin the less so.

Mechanism of the Shwartzman Phenomenon

In 1946 the late Dr. E. Martins da Silva and I studied the mechanism of production of the Shwartzman phenomenon, assuming the idea that disintegration of microthrombi of leucocytes and platelets might be the first step in the production of the haemorrhagic skin injury peculiar to this phenomenon. The predominant idea of the mechanism of production of thrombocytopenic purpura is that the presence of a certain level of circulating platelets is necessary to stop haemorrhages. We had assumed, as a working hypothesis, that clumping of platelets and their disintegration at the level of the capillary bed actually is the *cause* of the haemorrhagic symptoms, not the *cure*. By injecting intracutaneously in several places in the rabbit skin an antiplatelet serum, prepared according to Bedson (1922), we could follow the course of the phenomena leading to the local haemorrhages.

The technique used was as follows. Pieces of skin were cut with a sharp knife and thrown into a 3.8% solution of sodium citrate. By making impressions over slides and staining with Giemsa we could detect enormous well-formed clumps of platelets very soon after the local injection of the antiplatelet serum. Immediately before the onset of the haemorrhage these clumps appeared to undergo lysis and disintegration. From these observations it appeared likely that products derived from platelets or leucocytes would activate a factor in the blood that might contribute to the haemorrhagic effect. In another series of experiments Dr. Martins da Silva injected intracutaneously a suspension of platelets into a rabbit immunized by repeated injections of the same material. At the place of injection of the platelet suspension there developed a haemorrhagic spot. This interesting effect was greatly intensified by adding calcium to the platelet suspension, suggesting that the citrate used for collecting the platelets was to a certain extent inhibiting the reaction.

Further experiments have indicated that such a mechanism might underlie the production of the Shwartzman phenomenon (see Table). Rabbits were prepared by injecting intracutaneously 0.2 ml. of active meningococcus filtrate. Twenty-four hours later, instead of injecting the same filtrate intravenously, a potent antiplatelet serum was injected. The rapidity of development of the haemorrhagic process at the sites previously prepared with the filtrate was actually greater than that observed with the filtrate itself. The lesion was, as a rule, severer and larger with the serum than with the filtrate. Therefore a clumping of platelets at the prepared area, with the consequent lysis, would be enough to produce a haemorrhagic effect leading to necrosis and scar formation as in the typical Shwartzman phenomenon.

Effect of Antiplatelet Serum Upon Experimental Purpura (Shwartzman Phenomenon)

No. of Rabbits	Previous Treatment of Skin	Eliciting Injection (Intravenously)	Results and Observation
22	Meningococcus filtrate (0·2 ml.)	Antiplatelet serum (0·25 to 2·0 ml.)	0 (3); + (6); ++ (1); +++ (4); ++++ (8)
3	" " "	Glycogen (500 mg.)	++ (2); +++ (1)
3	Meningococcus filtrate *plus* antiplatelet serum	" "	0 (3); petechiae over the skin but no typical S.P.
4	" " "	Antiplatelet serum, then meningococcus filtrate	0 (3); " "
5	" " "	Antiplatelet serum, then glycogen (500 mg.)	0 (3); " " 0 (2); 0 (2); petechiae over the skin but no typical S.P.

0 = no typical Shwartzman reaction; + = a few petechiae localized over the prepared skin area; ++ = more redness turning brown, and more haemorrhagic spots over the prepared skin area; +++ and ++++ = strong Shwartzman reaction with the typical chocolate colour evolving into necrosis in the subsequent days. Glycogen from liver was shown by Bier and Amaral (1946) to elicit the Shwartzman reaction, and this was confirmed in these experiments. The antiplatelet serum injected simultaneously with the filtrate, 24 hours before eliciting the phenomenon with the serum or the filtrate or glycogen, prevented entirely the development of a typical Shwartzman reaction. The petechiae scattered over the skin were a typical reaction towards the antiplatelet serum. S.P. = Shwartzman phenomenon.

If the antiplatelet serum was injected *before* the preparation of the skin area in such a way that 24 hours later the rabbit was "deplateletized," the development of the phenomenon by the injection of the bacterial filtrate was inhibited. As a consequence of the injection of the antiplatelet serum itself, the animal showed petechiae scattered all over the body. Sometimes these haemorrhagic spots were severe and the animal died, but there was no indication of the development of a typical Shwartzman reaction upon the prepared areas. Therefore the *presence* of platelets, and not their absence, appeared to be an important factor in the development of this experimental purpura.

More recently Stetson (1951) analysed the microscopical appearance of areas of rabbit skin submitted to the Shwartzman phenomenon and could demonstrate the presence of such microthrombi of leucocytes and platelets. It seems probable that, as a consequence of this clumping of leucocytes and platelets and their disintegration, a factor or factors opposing haemostasis are set free or activated, thus leading to the haemorrhagic spot. That these factors might be histamine and the fibrinolytic enzyme of the blood was suggested by separate experiments (Rocha e Silva, 1950).

Liberation of Histamine by Anaphylatoxin

The success of the "cellular theory" appeared to relegate to a secondary plan the blood-borne "serotoxin" or "anaphylatoxin," and yet the strong similarity between the symptoms produced by it and those of anaphylactic shock in the guinea-pig would indicate that both phenomena have a common denominator. According to Dale and Kellaway (1922) anaphylatoxin would be more concerned with the so-called anaphylactoid phenomena, and yet these phenomena are so strongly evocative of the anaphylactic ones that a common mediator should still be found for them. The idea that cell injury might constitute this common mediator was rather unsatisfactory, since one would have to explain what "cell injury" is, thus adding another complication to the chain of evidence leading to an adequate explanation of the mechanism of action of the antigen upon the sensitized animal or of the blood-borne toxin, the anaphylatoxin of Friedberger and Bordet. The problem was to know why anaphylatoxin, which did not contain preformed histamine, should produce a shock that is indistinguishable from that produced by histamine itself or by the tissue histamine released during anaphylactic shock.

The key to this problem was provided by a paper published by Hahn and Oberdorf (1950), who demonstrated that antihistamines prevent the shock produced in guinea-pigs by the injection of an anaphylatoxin prepared by incubating guinea-pigs' serum with inulin. Following this lead we started a systematic study of the mechanism by which anaphylatoxin produces its effects in the guinea-pig. A preliminary report has been made (Rocha e Silva, Bier, and Aronson, 1951). The anaphylatoxin was prepared by incubating guinea-pig serum with agar according to Bordet's method. After centrifuging off the agar, the supernatant fluid was perfused through an isolated guinea-pig lung previously washed out by a long flow of warm Tyrode's solution. The rate of perfusion was somewhat faster (15 to 20 ml. of Tyrode's solution a minute) than in the usual experiments, and therefore the few millilitres of an anaphylatoxin injected into the cannula were in contact with the lung cells for only a short time. Despite this brief contact, considerable quantities were released almost instantaneously, the peak corresponding to the first one or two minutes of perfusion. This rate of release, as well as

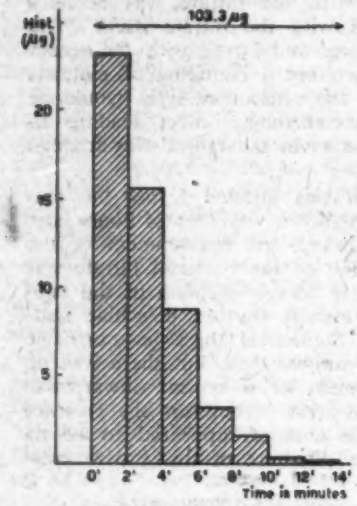

FIG. 2.—Discharge of histamine from a guinea-pig lung perfused with 4 ml. of dialysed and agar-activated serum of the guinea-pig. Total output of histamine in 12 minutes' perfusion = 103.3 µg.

the total amount released, was entirely different from that of similar experiments in which the sensitized lung was perfused with the antigen, in the absence of blood. As much as 47 µg. of histamine was released in the first two minutes in an experiment in which the total amount released was 103 µg. in 10 minutes of perfusion (Fig. 2).

In three experiments in which the serum was incubated with agar for one hour the range of total histamine appearing in the perfusates in six-minute experiments was 14.3 to 32.6 µg. (average, 20.7 µg.). On a second injection of exactly the same material an additional amount was obtained, ranging from 9.7 to 12.0 µg. (average, 10.4 µg.), as shown in Fig. 3. When the serum was heated before activation by agar, one hour at 60° C. was enough to render it incapable of activation. If heating was applied *after* incubation the resulting activated material was reduced to one-half after heating for an hour at 65 to 70° C., thus showing that the releasing substance (serotoxin) is somewhat more resistant to heat. If, however, the activated material was heated in the presence of 70% ethyl alcohol, serotoxin was completely destroyed. It

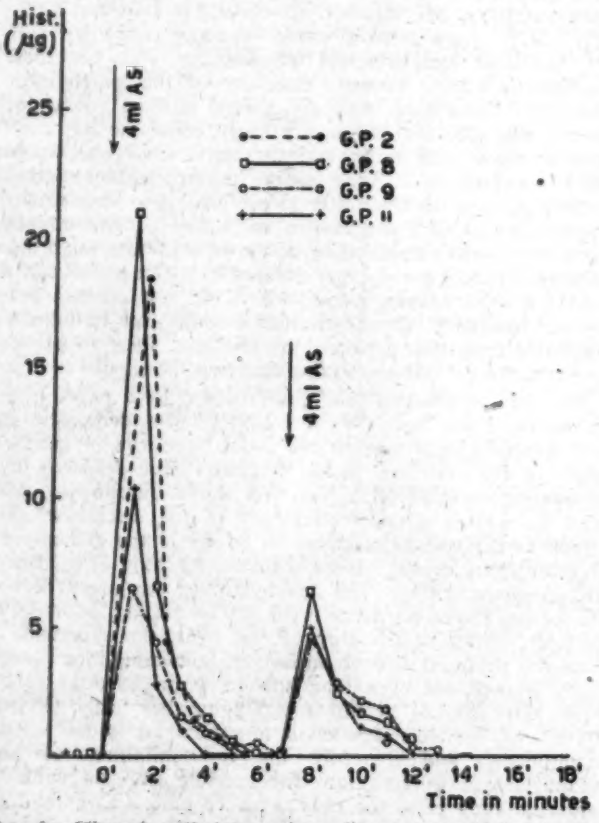

FIG. 3.—Histamine discharges from four guinea-pig lungs perfused with Tyrode's solution. At the arrows, 4 ml. of agar-activated guinea-pig serum injected. The first injections released about twice as much histamine as the second ones.

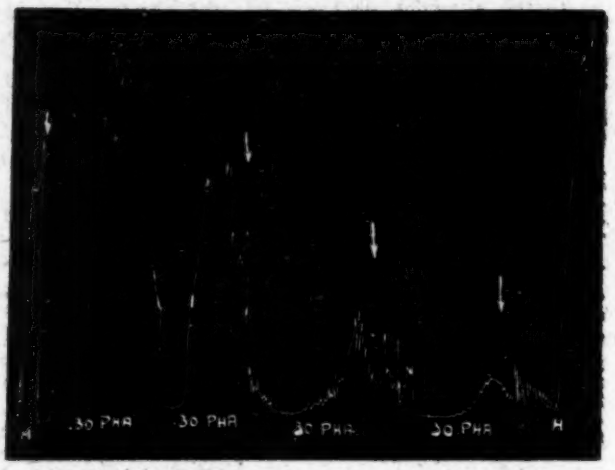

FIG. 4.—Isolated guinea-pig gut. Three successive additions of 0.3 ml. of rat-heparinized plasma (PHA) incubated with agar (rat anaphylatoxin). Note desensitization of the gut towards the histamine-releasing activity of that material. H = 0.2 ml. of a 1 in 2 million histamine.

appears beyond doubt that the serotoxin is connected with the non-dialysable part of the serum which is precipitated in the cold by 70% ethyl alcohol, and that it is not precipitated by half-saturation with ammonium sulphate.

Serotoxin prepared from guinea-pig serum, however, is not very potent. According to Novy and De Kruif (1917), a much more potent anaphylatoxin can be obtained by incubating the serum of the rat with agar, and this was confirmed in our laboratory. About 1 ml. of rat serum incubated with agar is equivalent to 3–4 ml. of guinea-pig serum. With rat serum we have been able to demonstrate that the formed anaphylatoxin has a striking effect on the isolated guinea-pig gut. A piece of gut is suspended in 7 ml. of Tyrode's solution in Dale's apparatus. Before incubation, 0.2 ml. of rat serum has no effect upon the gut. If, however, the serum is mixed with agar and 0.3 ml. of the mixture is added to the bath after increasing intervals of time, one can see (Fig. 4) that a strong contraction occurs after four to six minutes' incubation, thus showing that the time of activation of the serum is considerably shorter than the incubation time routinely used for the preparation of the anaphylatoxin. That the response of the gut is due to a release of histamine from the muscle itself can be demonstrated by the fact that after three or four additions of the same dose the muscle becomes desensitized, and that antihistamines stop this reaction.

Mechanism of Anaphylatoxin Formation

Activation of the serum by agar is possibly an enzymatic reaction, since heating at 60° C. for one hour completely inhibits the activating process. The nature of the chemical reaction that brings about the release of serotoxin is a subject for still further research. It has been assumed that the reaction is proteolytic in nature, consequent upon the removal of serum antitryptase and upon activation of the naturally occurring serum protease. This view was challenged by Dale and Kellaway (1922) on the ground that no change in amine nitrogen took place after incubation of the serum with agar. In our laboratory, attempts to demonstrate an increase in non-protein nitrogen also failed. Any attempt to demonstrate the increase in proteolytic activity by estimations of variations of viscosity of gelatin also failed.

But, while the intimate mechanism of the process is still unknown, we have a few data that might throw light upon it. If instead of serum we take citrated plasma, no activation occurs. Citrate appears to prevent the whole process of anaphylatoxin formation if put into contact with the blood at the moment it is collected (Fig. 5). Calcium added to the citrated plasma before the addition of agar will

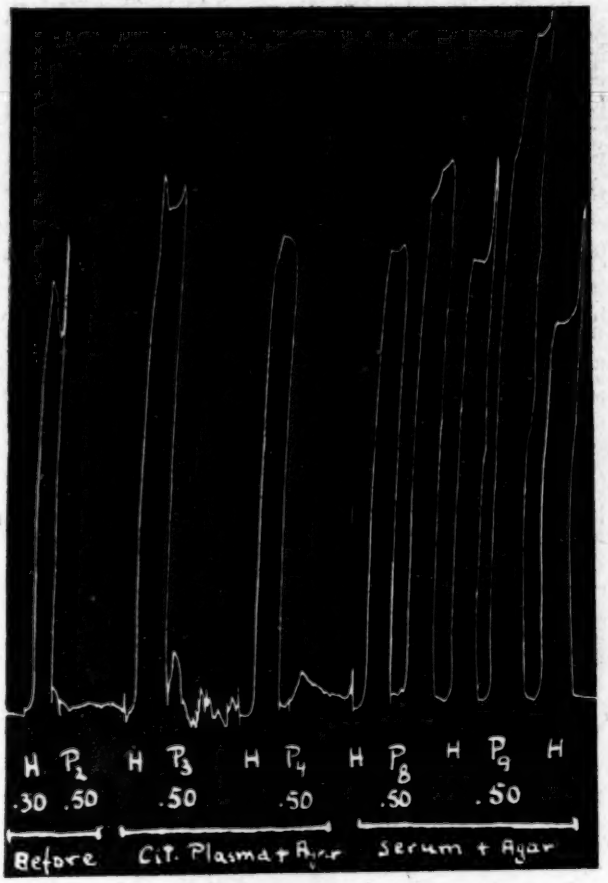

FIG. 5.—Isolated guinea-pig gut. Assay of the perfusates of a guinea-pig lung, before (P_2) and after (P_3 and P_4) the injection of citrated plasma submitted to incubation with agar. No histamine discharge was observed. P_8 and P_9 are the perfusates collected after the injection of serum activated by incubation with agar.

restore to only a very slight extent the capacity of being activated. It appears that citrate produces a somewhat irreversible change in the blood that makes it unsuitable for activation by agar. If, however, citrate is added *after* activation, no change in histamine-releasing activity can be demonstrated, thus showing that it is the process of activation that is disturbed by citrate. Added to guinea-pig serum, citrate still inhibits to a certain extent the process of activation (Fig. 6), and the addition of calcium restores only in part the ability of the serum to be activated.

This striking effect of citrate seems to indicate that a certain *quid*, or "factor Q," comes from the platelets and that even in serum its release may be prevented by the addition of citrate. This hypothesis would imply that even in serum the products derived from platelets are still in a form that is not available for the process, and that further disintegration, which is hindered by citrate, would be necessary to release the full amount of "factor Q." Although speculative, this explanation of the effect of citrate is the simplest one that might fit the experimental data so far obtained. For the irreversibility of the citrate effect we have no explanation to offer, but mention should be made of the results obtained by McIntire *et al.* (1949) on the release of histamine from cells to plasma in samples of rabbit's blood in experiments with the antigen. If it is the same factor that is activated by agar, or by the antigen in the sensitized rabbit's blood, a few differences in the process of activation might be pointed out. Heparin, which prevented the release of histamine in the case of rabbit's blood samples, was entirely unable to inhibit the activation of anaphylatoxin by agar.

Versene (ethylenediamine tetracetic acid), which is a powerful remover of calcium ions from the blood, rendering it incoagulable, was able to prevent its activation by agar. On the other hand, the removal of calcium ions by passing the blood through a cationic exchanger resin ("dawex 50") did not destroy its capacity of being activated by agar, although the blood remained incoagulable. These facts would induce one to study more thoroughly the relationship between the process of anaphylatoxin formation and the clotting of the blood. A complete separation of both phenomena could be achieved. In the first place, if calcium is added to citrated plasma it will clot, although the cation would restore, though only to a slight extent, the capacity of the resulting serum to be activated. It appears more likely that citrate produces a somewhat stronger protection towards platelets than that afforded by the simple removal of calcium, and that "factor Q," which probably comes from those elements of the blood, is distinct from the thromboplastic agent operative in blood-clotting. There are, of course, a few alternatives to explain the effect of citrate, but the one presented here seems to be more in accordance with the many facts previously described.

Citrate Therapy

A few practical conclusions might be drawn from these experiments. The striking effect of citrate in inhibiting anaphylatoxin formation, as well as the histamine release from dog's liver, induced us to try the local application of citrate upon several kinds of dermatitis that might be ascribed to an allergic cause. We have on a few occasions observed the favourable effect of an isotonic solution of citrate (3.8 to 4% solution of trisodium citrate) upon several types of allergic dermatitis.

A girl chemist who had a long-standing eczema extending over two-thirds of the right forearm showed striking

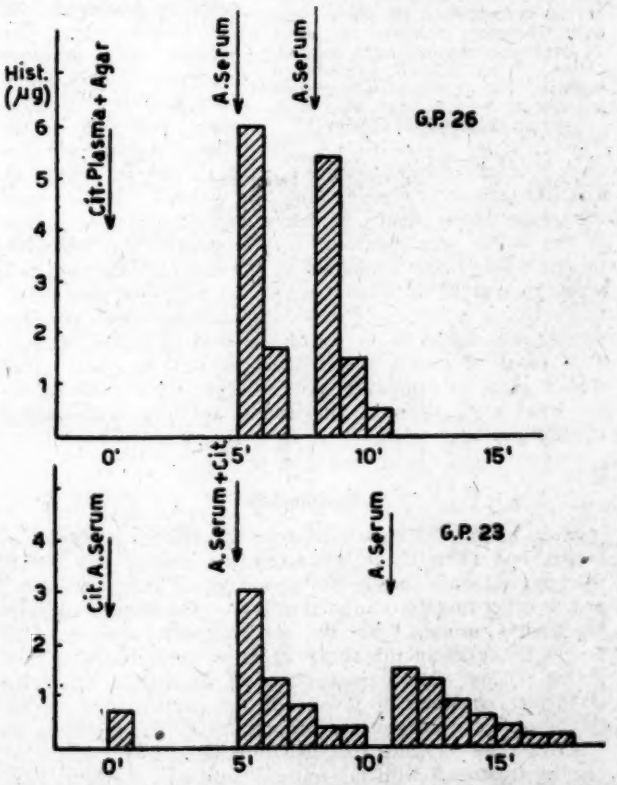

FIG. 6.—The plasma collected from citrated blood was not activated by agar (upper diagram) although two injections of activated serum (A. Serum) produced the usual discharges. Even when added to serum, before the agar, citrate somehow hindered the process of activation, although when added after agar activation (A. Serum+Citrate) there was no inhibitory effect (lower diagram).

improvement after applying citrate for four days and complete disappearance of the skin lesions in less than a week. A man who had developed an extremely severe dermatitis extending over both arms and thighs on handling insecticides was advised to apply the citrate lotion intermittently. When he started this treatment the skin lesions were heavily contaminated by scratching and had a bullous erythematous aspect. After one week's application of the citrate solution subsidence of the skin lesions was almost complete, and after two weeks only a few small scattered bullae could be seen in the wrist and cheeks.

Some other minor cases of allergic dermatitis were completely relieved after a few days' application of the 3.8% solution of trisodium citrate. I had also the opportunity of applying the citrate therapy to an allergic dermatitis that had developed in my own thumb, following all the steps of citrate action. The thumb presented extensive bullae (indicated by arrows in Fig. 7*a*), as well as extensive desquamation extending over an area of 4 to 5 cm.[3] These lesions were the result of a slow process that took about three months to reach the stage presented in Fig. 7*a*. After applying the citrate lotion for three days a definite improvement could be observed. At the points where the process was developing more acutely, small haemorrhages took place, followed by an almost immediate relief of the subjective and objective symptoms. Instead of itching, a rather reassuring burning sensation was felt. In one week the whole process had completely stopped and cicatrization of the bullae was apparent. Erythrodermia was intensive, this probably being explained by the fact that the skin was much thinner at the region where the intensive desquamation took place before. Fig. 7*b*, showing only slight erythrodermia, was taken 14 days after the start of citrate therapy. Two cases of severe facial acne, as well as some other minor cases of possible skin allergy, were relieved by the local application of an isotonic solution of trisodium citrate.

(*a*) (*b*)

FIG. 7.—Allergic dermatitis (*a*) developed in three months, apparently as the consequence of the contact with laboratory animals; (*b*) same 14 days after the intermittent application of an isotonic solution of sodium citrate (3.8%). The arrows indicate a deep bullous process in (*a*) and its cicatricial spot in (*b*).

Conclusion

Much more work should be done by experienced dermatologists and allergists in extending the use of this citrate therapy, not only locally but as sprays, to cases of asthma and to other manifestations of allergy. The idea of employing citrate resulted from the experimental evidence of its potent effect as an inhibitory agent in the process of histamine release. Its therapeutic effect in allergic dermatitis is further evidence in favour of the participation of the factor of histamine release present in normal blood in an inactive state—a state that can be changed into an active one by treatment with the antigen–antibody complex, agar, inulin, starch, etc.—in the so-called anaphylatoxin or serotoxin. Since citrate appears to stop the whole process of activation it would constitute a potentially more efficient instrument than symptom-relieving agents such as the antihistamines. Future research and clinical trials will decide whether the credit here given to citrate is justified.

BIBLIOGRAPHY

Arthus, M. (1903). *C.R. Soc. Biol., Paris*, **55**, 817.
Bartosch, R., Feldberg, W., and Nagel, E. (1932). *Pflügers Arch.*, **230**, 129.
Bedson, S. P. (1922). *J. Path. Bact.*, **25**, 94.
Bier, O., and Amaral, J. P. (1945). *Mem. Inst. Butantan*, **18**, 33.
Bordet, J. (1913). *C.R. Soc. Biol., Paris*, **74**, 877.
Dale, H. H. (1913). *J. Pharmacol.*, **4**, 517.
—— (1920). *Proc. roy. Soc. B*, **91**, 126.
—— and Kellaway, C. H. (1922). *Philos. Trans. B*, **211**, 273.
Daly, I. de B., Peat, S., and Schild, H. O. (1935). *Quart. J. exp. Physiol.*, **25**, 33.
Dragstedt, C. A., De Arellano, M. R., Lawton, A. H., and Youmans, G. P. (1940). *J. Immunol.*, **39**, 537.
—— Wells, J. A., and Rocha e Silva, M. (1942). *Proc. Soc. exp. Biol., N.Y.*, **51**, 191.
Emmelin, N., Kahlson, G. S., and Lindström, K. (1941). *Acta physiol. scand.*, **2**, 78.
Friedberger, E. (1909). *Z. ImmunForsch.*, **2**, 208.
Friedeman, U. (1909). Ibid., **2**, 591.
Hahn, F., and Oberdorf, A. (1950). Ibid., **107**, 528.
Holmes, C. A., Ojers, G., and Dragstedt, C. A. (1941). *Proc. Soc. exp. Biol., N.Y.*, **46**, 576.
Katz, G. (1940). *Science*, **91**, 221.
Keysser, F., and Wassermann, M. (1911). *Z. Hyg.*, **68**, 335.
McIntire, F. C., Roth, L. W., and Richards, R. K. (1949). *Amer. J. Physiol.*, **159**, 332.
Nathan, E. (1913). *Z. ImmunForsch.*, **17**, 478.
Nolf, P. (1910). *Arch. Physiol.*, **10**, 37.
Novy, F. G., and De Kruif, P. H. (1917). *J. infect. Dis.*, **20**, 589.
Ojers, G., Holmes, C. A., and Dragstedt, C. A. (1941). *J. Pharmacol.*, **73**, 33.
Otto, R. (1907). *Münch. med. Wschr.*, **54**, 1665.
Portier, P., and Richet, C. (1902). *C.R. Soc. Biol., Paris*, **54**, 170.
Rocha e Silva, M. (1950). *Ann. N.Y. Acad. Sci.*, **50**, 1045.
—— Aronson, M., and Bier, O. (1951). *Nature*, **168**, 465.
—— and Graña, A. (1946). *Arch. Surg., Chicago*, **52**, 713.
—— Scroggie, E., Fidlar, E., and Jaques, L. B. (1947). *Proc. Soc. Exp. Biol., N.Y.*, **64**, 141.
Rose, B., and Browne J. S. L. (1941). *J. Immunol.*, **41**, 403.
Schild, H. O. (1939). *J. Physiol.*, **95**, 393.
Scroggie, A. E., and Jaques, L. B. (1949). *J. Immunol.*, **62**, 103.
Stetson, C. A. jun. (1951). *J. exp. Med.*, **93**, 489.
Ungar, G., and Parrot, J. L. (1936). *C.R. Soc. Biol., Paris*, **123**, 676.

THE ENZYME AT SYMPATHETIC NERVE ENDINGS*

BY

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At the endings of the vagus and of other nerves, where acetylcholine is liberated to transmit the impulse to the end organ, the enzyme cholinesterase is found. The importance of cholinesterase in controlling the response to the nerve impulse is well known from the action of neostigmine. Knowledge of the working of sympathetic nerves has been much behind that of cholinergic nerves until recently, when it received a great impetus from the discovery of *nor*adrenaline in sympathetic nerves by Von Euler (1946). Other workers, first Peart (1949), and later Mann and West (1950, 1951), have shown that *nor*adrenaline is released when sympathetic nerves are stimulated.

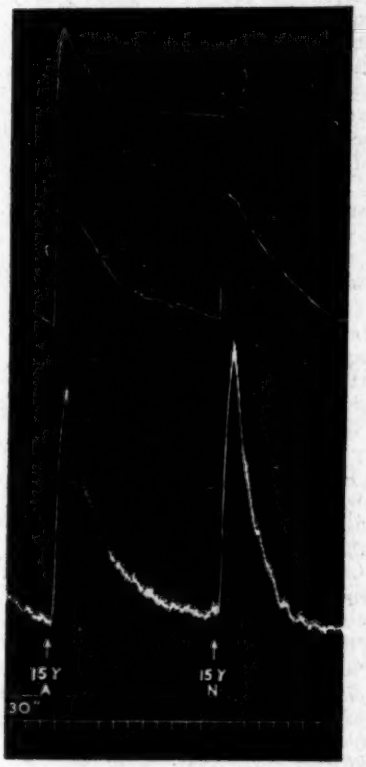
*Nor*adrenaline being established as the transmitter, the question arises what enzyme destroys it. Evidence has been accumulating that it is amine oxidase, an enzyme discovered by Hare (1928). Attention was first drawn to amine oxidase as an enzyme concerned with the destruction of adrenaline by the work of Blaschko, Richter, and Schlossmann (1937) on the one hand, and by the work of Gaddum and Kwiatkowski (1938) on the other. The former showed that adrenaline, among other amines, was a substrate of the enzyme, but that ephedrine was not, and that ephedrine indeed inhibited the action of the enzyme on adrenaline. Gaddum and Kwiatkowski demonstrated that ephedrine potentiated the action of adrenaline in causing constriction of the vessels of the rabbit ear, and they suggested that this

*A lecture delivered at Cornell Medical College on April 23, 1951.

potentiation could be explained if amine oxidase were present in the vessels, and if its action there on adrenaline was inhibited by ephedrine.

A *Nor*adrenaline Hypothesis

So the matter rested until 1949, when an approach was made from a different direction. In work on the nictitating membrane of the cat's eye Bülbring and Burn (1949) found that *nor*adrenaline was much weaker in causing contraction than adrenaline, though if the membrane was denervated both *nor*adrenaline and adrenaline were of similar and greater potency, as shown in the accompanying illustration.



Record taken from spinal cat. The upper tracing shows contractions produced in the normal nictitating membrane. The middle tracing shows contractions in the denervated nictitating membrane. The lower record is the blood pressure. The first injection is 15 μg. of adrenaline. The second injection is 15 μg. of *nor*adrenaline.

Burn and Hutcheon (1949) observed that the same relations existed for dilatation of the pupil. *Nor*adrenaline when injected intravenously had much less effect than adrenaline in dilating the normal pupil: a dose of *nor*adrenaline 12–15 times as great was necessary to produce the same effect as a dose of adrenaline. The denervated iris, however, which was more sensitive than the normal iris to adrenaline, responded to *nor*adrenaline very much as it did to adrenaline.

On the blood vessels of the rabbit ear the constrictor effect of *nor*adrenaline was shown by Luduena *et al.* (1949) and by Gaddum *et al.* (1949) to be weaker than that of adrenaline. Burn and Robinson (1951a) compared the effect of *nor*adrenaline and adrenaline in 29 experiments and obtained a mean figure of 5.9 as the amount of *nor*adrenaline which was required to produce the same constriction as a unit amount of adrenaline.

Thus in all three tissues—the nictitating membrane, the iris, and the rabbit ear vessels—*nor*adrenaline was found to be much weaker than adrenaline, a conclusion which was surprising, since *nor*adrenaline was known to be the sympathetic transmitter, and therefore likely to be at least as potent as adrenaline, if not more potent. The fact that after denervation of the nictitating membrane and iris this weakness of *nor*adrenaline largely disappeared suggested that the weakness was only apparent. Burn and Hutcheon therefore supposed that there might be an enzyme at the sympathetic nerve ending which decreased in amount after denervation; it is known, for example, that cholinesterase diminishes in the superior cervical ganglion after the preganglionic fibres have been cut (Brücke, 1937). This enzyme at the sympathetic nerve ending, being presumably designed to destroy the transmitter *nor*adrenaline, might have a greater affinity for it than for adrenaline, and, if so, might destroy *nor*adrenaline given by intravenous injection more readily than adrenaline. The presence of the enzyme might thus create the appearance that *nor*adrenaline was a much weaker substance.

Amine Oxidase

The foregoing hypothesis has now been tested in various ways, and the results have supported it. The first question which arose was the identity of the enzyme. In view of the work of Blaschko and of Gaddum, already described, it was natural to think of amine oxidase. This idea was given strong support when Thompson and Tickner (1951) published their paper showing that this enzyme is present in all the blood vessels of the rabbit. Miss Robinson (1951) then showed that amine oxidase is also present in the nictitating membrane and in the iris of the cat.

The second question was whether amine oxidase destroys *nor*adrenaline more rapidly than it destroys adrenaline. The earlier observations of Blaschko, Richter, and Schlossmann (1937) did not suggest this. The rate of oxygen uptake measured in the Warburg apparatus when amine oxidase acted on adrenaline was similar to the rate when it acted on *nor*adrenaline. Accordingly, experiments were carried out in which amine oxidase was allowed to act on a mixture of equal amounts of adrenaline and *nor*adrenaline, and the proportion of the two amines in the mixture was determined as the oxidation continued. It was found that *nor*adrenaline disappeared more rapidly than adrenaline and that the percentage of adrenaline in the unoxidized portion of the mixture steadily rose (Blaschko and Burn, 1951; Burn and Robinson, 1951). Thus evidence was obtained that amine oxidase destroys *nor*adrenaline more rapidly, as the hypothesis required. Recently Bain and Batty (1952) have made a careful statistical study of the rate of oxidation of adrenaline and of *nor*adrenaline (separately) in blood in the presence of liver slices. They found that, in these conditions also, the rate of oxidation of *nor*adrenaline is more rapid than that of adrenaline, and their findings have enabled them to calculate what changes would occur during the oxidation of a mixture of equal parts of the two substances. The calculation so obtained agreed fairly well with the results already described.

Effect of Denervation

The next step in the investigation was to test the effect of denervation on the amount of amine oxidase, to see if the amount declined. Such a decline would explain the greater effect of adrenaline and the much greater effect of *nor*adrenaline in the denervated nictitating membrane and iris.

Denervation of the nictitating membrane and iris was effected by removing the right superior cervical ganglion. Denervation of vessels was effected by removing the right stellate ganglion, which supplied the sympathetic fibres to the vessels of the foreleg. These operations were performed aseptically at various intervals before the cats were killed. The changes in the nictitating membrane were examined in 57 cats, and the mean results are shown in Table I. During the first period, up to 10–12 days after denervation, the amine oxidase fell to a mean figure of 66% of the normal. Thereafter the amine oxidase rose steadily, to regain the normal figure in four to five weeks.

TABLE I.—*Amine Oxidase in Denervated Nictitating Membrane as Percentage of Normal*

Period of Denervation	No. of Cats	Mean Amount of Amine Oxidase
8–9 days	9	71
10–12 ,,	7	66·5
16–19 ,,	20	73
21 ,,	12	88
25–28 ,,	7	92
33 ,,	2	101

There was, however, much variation in the fall in the amine oxidase in different cats. In some it fell to 40% or less, while in others there was little or no fall. At first it seemed that the variation was so great that the increased sensitivity of the denervated membrane to *nor*adrenaline could not be accounted for by the fall in amine oxidase. A

comparison was therefore made of the increase in sensitivity of the denervated membrane with the fall in amine oxidase. The increase was found to be significantly correlated with the fall in amine oxidase in 10 cats examined within 8–12 days after denervation (Burn and Robinson, 1952).

For the periods after denervation longer than 12 days the correlation between increased sensitivity of the membrane to *nor*adrenaline and fall in amine oxidase was not significant. The increased sensitivity of the denervated membrane persisted (though it declined), while the amine oxidase returned towards normal.

In the blood vessels, also, a loss of amine oxidase after denervation was observed; the results were on the whole similar to those in the nictitating membrane in suggesting that the loss of amine oxidase occurred during the early days of denervation, and that the amine oxidase was then gradually restored. The results are shown in Table II. In making these experiments vessels from several cats were pooled. Table II shows that the agreement between figures for normal right leg vessels and normal left leg vessels was satisfactory, while the denervated right leg vessels contained much less enzyme.

TABLE II.—*Percentage of Amine Oxidase in Vessels of Right Foreleg in Terms of Amount in Left Foreleg Vessels*

No. of Cats	Days Denervated	Right Leg	
		Normal	Denervated
6	—	103	—
4	—	86	—
5	—	105	—
5	9	—	22
6	21	—	71
4	28	—	57

In the iris no observations were made earlier than 15 days after denervation, and it is possible that the point of greatest fall in amine oxidase was missed. The mean figure for the period 15–26 days after denervation was 77% of the amount in the corresponding normal pupil. This was the mean figure for 36 cats.

Enzyme Inhibitors

The foregoing evidence of changes in amine oxidase produced by denervation is further strengthened by evidence from the effect of ephedrine and cocaine, which inhibit the enzyme *in vitro*. As already described, Gaddum and Kwiatkowski (1938) found that ephedrine potentiated the effect of adrenaline and of sympathetic stimulation in the rabbit ear vessels and in the nictitating membrane. Burn and Robinson (1951) found that the constrictor effect of *nor*adrenaline in rabbit ear vessels became much stronger in relation to that of adrenaline when ephedrine was added to the perfusing fluid; this change was consistent with the view that the relative weakness of *nor*adrenaline was due to its more rapid destruction by amine oxidase.

Cocaine increases the response of the normal nictitating membrane to *nor*adrenaline, but has relatively little effect on the response of the denervated membrane. When 8 mg. of cocaine was given by intramuscular injection to spinal cats, after making observations similar to those shown in Fig. 1, the contraction of the normal nictitating membrane in response to *nor*adrenaline increased and became about equal in size to the contraction of the denervated membrane. Whatever the ratio of the contraction in the denervated membrane to that in the normal membrane before cocaine was given, the ratio was approximately =1 after cocaine was given. Observations in some respects parallel have been made by Innes and Kosterlitz (1951) on the effect of cocaine and of denervation on the increase in heart rate produced by *nor*adrenaline. Almost the only findings which are inconsistent with the view that the effect of cocaine is to inhibit amine oxidase are that certain other substances which inhibit amine oxidase *in vitro*, such as cinchocaine and stilbamidine have not been found to act like cocaine in the body. A careful study of these anomalies has not yet been made, but, as Albert (1951) has pointed out, for a substance which acts *in vitro* to act also *in vivo* its structure must confer the correct adsorption and partition properties both during transit to the site and at the site itself.

Thyroid Activity and Amine Oxidase

The Liver.—Amine oxidase has long been known to be present in the liver, and its importance for glycogenolysis has recently been demonstrated. In hyperthyroidism the sugar tolerance is low, and in animals fed with thyroid the effect of adrenaline in raising the blood sugar is abnormally great. Burn and Marks (1925) showed that rabbits given 0.2 g. of thyroid daily for two weeks responded to the subcutaneous injection of adrenaline with a much greater hyperglycaemia than before. Spinks and Burn (1952) have now found that when rabbits are thus fed with thyroid there is a significant fall in the amount of amine oxidase in the liver (calculated per milligram liver nitrogen). Likewise there is a rise in amine oxidase in the liver after thyroidectomy, which, though not statistically significant in the rabbit, is significant in the rat. The abnormal rises in blood sugar seen in hyperthyroidism, therefore, are probably explained by a fall in amine oxidase in the liver, and the results further emphasize the importance of amine oxidase in controlling the magnitude of sympathetic effects.

The Blood Vessels.—In hyperthyroidism another abnormal response to adrenaline has long been known—namely, an abnormally great rise in blood pressure. This increased effect is the basis of the Goetsch test (1918) for hyperthyroidism. Spinks (1952) has recently examined the amine oxidase present in the aorta of eight thyroid-fed rabbits, comparing it with the amount in eight controls. He found that the amine oxidase was significantly lower in the thyroid-fed animals. He also found that the blood pressure when measured in the carotid artery after anaesthetizing the rabbits by a standard procedure was significantly higher in the thyroid-fed animals, and, moreover, that the amount of adrenaline required to produce a certain rise of blood pressure was lower in the thyroid-fed animals. (The significance here was given by $P=0.06$.) These results require extension, but they make it highly probable that changes in blood pressure occurring as a result of changes in thyroid activity are effected through changes in the amount of amine oxidase in the blood vessels.

The use of sodium or potassium thiocyanate to lower blood pressure is still common in the United States. This substance was shown by Astwood (1943) to diminish thyroid activity, and there are reasons for thinking (Burn, 1948) that it lowers blood pressure by its effect on the thyroid gland. Probably its administration is followed by a rise in amine oxidase in blood-vessel walls.

Discussion

The combined effect of the different pieces of evidence is to present a very strong, if not conclusive, argument that in the neighbourhood of the sympathetic nerve endings in the blood vessels, the nictitating membrane, and the iris there is an enzyme—amine oxidase—which exerts the same function as cholinesterase at the endings of cholinergic nerves. Amine oxidase is certainly present in these organs; it is an enzyme which destroys *nor*adrenaline more rapidly than adrenaline, and so its activity would explain the otherwise puzzling observation that *nor*adrenaline reaching the nictitating membrane and iris in the blood stream or the blood vessels in the perfusing fluid is so much weaker than adrenaline. The amount of amine oxidase falls in these organs after denervation. This observation is alone sufficient to prove that amine oxidase has some connexion with the sympathetic innervation. But when, in addition, the evidence shows that during the first ten days after denervation of the nictitating membrane the fall in the amount of enzyme is correlated with the increase in the sensitiveness of the membrane to *nor*adrenaline, the part played by the enzyme in

modifying the response of the organ to the sympathetic transmitter seems to be finally established. It is pleasant to point out that these observations are in full agreement with the evidence and views of Blaschko and his colleagues put forward in 1937 and of Gaddum in the following year. The action of cocaine seems to be similar to that of ephedrine and to consist also in an inhibition of amine oxidase.

The effect of thyroid feeding in diminishing the amine oxidase in the liver furnishes an explanation for old observations not only on the physiological but also on the clinical side. In the thyroid-fed animal adrenaline produces a greater hyperglycaemia than in the normal animal, and the work of Marks (1925) brought this fact into relation with the diminished sugar tolerance of hyperthyroid patients. Because of the fall of amine oxidase in the liver, the extent of the glycogenolysis which occurs as a result of a given sympathetic stimulus is supernormal.

Perhaps of greater import is the evidence that thyroid feeding causes a fall in the amine oxidase in the blood vessels, and that this fall is accompanied by a raised blood pressure and a raised sensitivity to the pressor action of adrenaline. These observations implicate amine oxidase in the control of blood pressure in the clearest manner, and show that changes in the amount of this enzyme or in the factors which modify its activity must be carefully considered in relation to hypertension.

Summary

At the vagus nerve endings and at motor nerve endings in skeletal muscle the enzyme cholinesterase is present. Evidence is shown that there is a corresponding enzyme, amine oxidase, around the sympathetic nerve endings in the blood vessels, the nictitating membrane, and the iris of the cat. This enzyme destroys the sympathetic transmitter, *nor*adrenaline, more rapidly than it destroys adrenaline. The enzyme declines in amount after denervation, and in the nictitating membrane during the first ten days the decline is proportional to the increase in sensitivity to *nor*adrenaline. Later the amount of enzyme is restored both in nictitating membrane and in the blood vessels.

The amount of amine oxidase in the liver is reduced by thyroid feeding and increased by thyroidectomy. These changes probably explain the greater hyperglycaemia which adrenaline produces in the thyroid-fed animal.

The amount of amine oxidase in the blood vessels is reduced by thyroid feeding. This is correlated with a rise in the blood pressure and an increase in the pressor effect of adrenaline.

REFERENCES

Albert, A. (1951). *Selective Toxicity*, p. 185. Methuen, London.
Astwood, E. B. (1943). *J. Pharmacol.*, **78**, 79.
Bain, W. A., and Batty, J. (1952). Communication to Pharmacological Society, January 5.
Blaschko, H., and Burn, J. H. (1951). *J. Physiol., Lond.*, **112**, 37P.
—— Richter, D., and Schlossmann, H. (1937). *Biochem. J.*, **31**, 2187.
Brücke, F. T. v. (1937). *J. Physiol., Lond.*, **89**, 429.
Bülbring, E., and Burn, J. H. (1949). *Brit. J. Pharmacol.*, **4**, 202.
Burn, J. H. (1948). *Background of Therapeutics*, p. 46. Oxford Univ. Press, London.
—— and Hutcheon, D. E. (1949). *Brit. J. Pharmacol.*, **4**, 373.
—— and Marks, H. P. (1925). *J. Physiol., Lond.*, **60**, 131.
—— and Robinson, J. (1951). *Brit. J. Pharmacol.*, **6**, 101.
—— —— (1952). *J. Physiol., Lond.*, **116**, 21P.
Euler, U. S. v. (1946). *Acta physiol. scand.*, **12**, 73.
Gaddum, J. H., and Kwiatkowski, H. (1938). *J. Physiol., Lond.*, **94**, 87.
—— Peart, W. S., and Vogt, M. (1949). Ibid., **108**, 467.
Goetsch, E. (1918). *N.Y. St. J. Med.*, **18**, 259.
Hare, M. L. C. (1928). *Biochem. J.*, **22**, 968.
Innes, I. R., and Kosterlitz, H. W. (1951). *Brit. J. Pharmacol.*, **6**, 651.
Luduena, F. P., Ananenko, E., Siegmund, O. H., and Miller, L. C. (1949). *J. Pharmacol.*, **95**, 155.
Mann, M., and West, G. B. (1950). *Brit. J. Pharmacol.*, **5**, 173.
—— —— (1951). Ibid., **6**, 79.
Marks, H. P. (1925). *J. Physiol., Lond.*, **60**, 402.
Peart, W. S. (1949). Ibid., **108**, 491.
Robinson, J. (1951). Ibid., **115**, 39P.
Spinks, A. (1952). Unpublished.
—— and Burn, J. H. (1952). *Brit. J. Pharmacol.*, **7**, 93.
Thompson, R. H. S., and Tickner, A. (1951). *J. Physiol., Lond.*, **115**, 34.

THE ANAEMIA OF HYPOPITUITARISM

BY

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The purpose of this paper is to present observations on some of the haematological changes which occur in hypopituitarism. A normochromic anaemia of moderate severity and refractory to treatment is usual in this syndrome (Sheehan and Summers, 1949), but examples of both hypochromic and hyperchromic anaemia are also recorded. In few of the recorded cases are details of absolute values given, and accurate classification of the anaemia is therefore impossible. One case of aplastic anaemia has been reported (Bloom and Bryson, 1948), and Addisonian pernicious anaemia has also been described (Witts, 1932). The diagnosis of severe hypopituitarism in these cases is, however, doubtful.

All the cases in the present study, with one exception, were typical examples of hypopituitarism due to postpartum necrosis of the anterior lobe, and had had amenorrhoea since their last delivery, absent pubic and axillary hair, cold-sensitivity, lowered basal metabolism, low 17-ketosteroid excretion, and typical responses to the insulin-sensitivity test. The exception was a case occurring in a man who had typical clinical and biochemical changes, but in whom the aetiology of the hypopituitarism was uncertain. Subsequent necropsy in one of these cases confirmed the clinical diagnosis.

Methods

The observations presented were made on 10 patients. All were observed as in-patients in the early stages, and the subsequent follow-up was done as out-patients. All the haematological investigations were made by me.

Blood for red-cell counts was obtained by venepuncture from an antecubital vein, using a dry sterilized syringe and needle. The blood was collected into a 5-ml. bottle containing Wintrobe's anticoagulant mixture (1.2 g. ammonium oxalate and 0.8 g. potassium oxalate dissolved in 100 ml. neutral distilled water). To prevent deterioration 1 ml. of 40% formalin was added to this mixture; 0.5 ml. was run into each bottle from a burette and allowed to dry. The blood was diluted in a Thoma haemocytometer pipette using Hayem's fluid (sodium chloride 1 g., sodium sulphate 5 g., corrosive sublimate 0.5 g., and distilled water 200 ml.).

The haemoglobin was estimated by means of a Spekker photo-electric absorptiometer, using a yellow-green filter with an optical density of 0.475; 100% by this method corresponds to 14.8 g. of haemoglobin per 100 ml.

Reticulocyte counts were made using equal parts of blood and a brilliant cresyl blue solution (consisting of one part of a saturated alcoholic solution of brilliant cresyl blue to five parts of a normal saline solution to which 0.4 g. of sodium citrate was added). After mixing of the blood and cresyl blue, smears were made, dried, and counterstained with Leishman's stain. The number of reticulocytes in 1,000 red cells was counted.

The mean corpuscular volume (M.C.V.), the mean corpuscular haemoglobin (M.C.H.), and the mean corpuscular haemoglobin concentration (M.C.H.C.) were determined by the methods of Price-Jones, Vaughan, and Goddard (1935).

The methods available for determination of the red-cell diameter are open to many inaccuracies. The value of the diffraction method of Pijper (1919, 1947) in the determination of red-cell diameter has recently been assessed by Hird (1949), who thought the method unreliable in esti-

mating macrocytosis except in the extreme upper range, greater than 8.5 μ, and of no value in assessing microcytosis.

The method of Price-Jones (1910), although considerably more accurate than diffraction methods, is extremely laborious and technically difficult. For these reasons no direct measurement of red-cell diameter was made. It was also considered that the cubic measurement of cell volume was a more accurate indication of cell size, providing spherocytosis was absent.

The usual gruel meal was given for assessing gastric acidity, specimens of gastric juice being collected at 15-minute intervals for three hours. At the end of 90 minutes 0.5 mg. of histamine acid phosphate was given.

Haematological Data

The haematological data in these cases are recorded in Table I, together with details of the duration of the disease, the basal metabolism, and the state of gastric secretion.

TABLE I.—*Blood Counts in Cases of Hypopituitarism*

Case No.	Time Since Onset (Years)	B.M.R. %	Cholesterol mg./100 ml.	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	M.C.H.C. %	Achlorhydria
Macrocytic Hypochromic Anaemia								
1	6			4·1	11·9	102	30	+
2	6	−40	190	3·2	9·6	104	30	+
3	17	−38	370	3·3	9·7	109	27	+
4	17	−42	360	3·5	9·4	110	30	+
5	31	−29	125	3·0	8·5	94	28	+
6	35		120	3·5	11·6	114	29	+
Normocytic Hypochromic Anaemia								
7	7	−45	380	3·8	9·1	92	26	+
8	15	−25	150	4·1	11·7	90	32	+
9	20	−44	80	4·7	10·6	85	27	Free acid
10	20	−46	191	4·2	12·0	88	32	+

For the purpose of classification an anaemia was regarded as macrocytic if the M.C.V. was greater than 94 μ^3, normocytic if between 78 and 94 μ^3, and microcytic if less than 78 μ^3. If the M.C.H.C. was less than 32% the anaemia was regarded as hypochromic (Wintrobe, 1946).

Macrocytic Hypochromic Anaemia.—In six cases the anaemia was macrocytic and hypochromic, the red-cell count ranging between 3 and 4.1 millions per c.mm. and the haemoglobin between 8.5 and 11.9 g. per 100 ml. The M.C.V. ranged between 94.3 and 113.6 μ^3. No polychromatic cells, no cells showing basophilic stippling, and no immature cells were seen in the stained films. Few anisocytes and poikilocytes were observed. Clinically three patients had marked myxoedematous features, and three moderate. Histamine-fast achlorhydria was present in all the cases in which this test was performed. The bone marrow was normoblastic in all cases.

Normocytic Hypochromic Anaemia.—There were four cases in this group, the red-cell count ranging between 3.8 and 4.7 millions per c.mm. and the haemoglobin between 9.1 and 12 g. per 100 ml. The M.C.V. ranged between 85 and 92.1 μ^3, and was in all cases near the upper limit of the normocytic range. No immature or polychromatic cells were seen in the stained films. Free hydrochloric acid was present in one case. The bone marrow was normoblastic in all cases. Clinically, two patients had myxoedematous features.

Achlorhydria.—Achlorhydria occurred in nine cases of hyperchromic anaemia recorded in the literature, but in four such cases normal gastric acidity was found; similarly, in cases of hypochromic anaemia occurring in hypopituitarism and recorded there were five instances of achlorhydria and four of normal gastric acidity. Achlorhydria was found in all but one of the cases studied in the present series.

Glossitis, Perlèche, Koilonychia.—Atrophy of the mucous membrane of the tongue with perlèche was observed only in Case 7, in which the anaemia was of normocytic type. There are very few reports in the literature of glossitis occurring in hypopituitarism, but cases are recorded by Means, Hertz, and Lerman (1940, Case 4), Fraser and Smith (1941, Case 2), and Caughey (1946). All these patients had a hyperchromic anaemia, but no details of cell size are given in the reports. There are no reports in the literature of either perlèche or koilonychia occurring in cases of hypopituitarism associated with anaemia.

Therapy

Various methods of treatment were tried in these cases, and the results of such therapy on the blood counts and haemoglobin are discussed.

Thyroid

All patients who had a macrocytic hypochromic anaemia had appearances resembling myxoedema. The basal metabolic rate in those cases in which the estimation was made was similar to the rate seen in myxoedema, and severe thyroid atrophy is one of the constant post-mortem findings in severe hypopituitarism. Thyroid deficiency might reasonably be deduced to cause part of the syndrome of hypopituitarism, and therefore thyroid extract was given to Cases 3, 4, and 6. The dose administered was 0.5 g. twice daily. This small dose of thyroid was given because of the possible risk of inducing an adrenal crisis, examples of which have been reported. The results of treatment are shown in Table II.

TABLE II

Case No.	Before Treatment				After Treatment			
	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	B.M.R. %	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	B.M.R. %
4	3·5	9·4	110	−42	3·6	9·6	90	−8
6	3·5	11·6	114		3·6	11·8	93	
3	3·3	9·7	109	−38	3·4	9·7	94·2	+4

The duration of treatment in Cases 4 and 6 was six months and in Case 3 ten months. No reticulocytosis was observed during the treatment. Although the changes in the red-cell count and the haemoglobin were not marked, there was a reduction in the size of the red cells as manifested by the M.C.V., and this was associated with a rise in the B.M.R. in the two cases in which observations on this were made. No investigations of the effect of thyroid was made in patients with a normocytic anaemia.

The effects of thyroid therapy in hypopituitarism have been reported frequently, but no constant pattern of response by the blood-forming tissues can be detected. Thus a fall in the red-cell count and haemoglobin was noticed by Boller and Goedel (1935, Case 1), Robertson (1945), and Daughaday *et al.* (1948, Case A. A.). On the other hand, van Balen (1939, Case 1) observed an initial rise in both the red-cell count and haemoglobin, but this was followed by a return to the starting levels within a month. Mallory (1940) noticed no change in the blood after thyroid had been given; Darley *et al.* (1944) also observed no improvement after administering thyroid, iron, and liver. A reduction in the mean corpuscular diameter from 8.7 to 8 μ was found by de Langen (1937, Case 1), but there was no change in the haemoglobin.

However much the clinical appearances, the basal metabolism, and the blood picture in hypopituitarism resemble those in myxoedema, thyroid extract does not seem to produce improvement in the blood in the macrocytic anaemia of hypopituitarism.

Testosterone

Testosterone propionate administered intramuscularly or implanted subcutaneously produces clinical improvement in most cases of hypopituitarism. Four patients have been treated in this way: in Case 4, 400 mg. of testosterone propionate was implanted subcutaneously in the abdominal

wall, and in Cases 1 and 5, 100 mg. of testosterone propionate was given intramuscularly each week for one month, when four 100-mg. pellets were implanted in the subcutaneous tissue of the abdominal wall. Neither of these patients had received any other form of treatment. Case 10 had previously received 1,250 mg. of "ferrivenin"; in this case also four 100-mg. pellets of testosterone propionate were implanted subcutaneously, and subsequently at three-monthly intervals. Treatment with thyroid extract had been given in Case 4; but none had been given for eight months before implanting testosterone. The results of treatment are shown in Table III.

TABLE III

Case No.	Before Treatment				After Treatment				
	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	M.C.H.C. %	R.B.C. mil./c.mm.	Hb g./100 ml.	M.C.V. μ^3	M.C.H.C. %	Duration of Treatment. Months
4	3·5	9·4	111	30·0	3·7	9·6	105	30	1
					4·9	13·6	87	33	2
10	4·2	12·0	88	32	4·8	13·6	88		3
					5·0	13·8	88		6
					4·9	13·8	88		9
1	4·1	11·9	102	29·7	4·1	11·9	101	29	4
5	3·0	8·5	90·3	29·3	3·7	10·3	90·7	30	1
					3·4	9·4	90·0	30	2

In Case 10 there was a small rise in both the red-cell count and haemoglobin, which had almost reached its maximum at the end of two months. In Case 5 there was a rise in the red-cell count and haemoglobin at the end of the first month, but a fall in both these values occurred at the end of the second month, although both the haemoglobin and the red-cell count were above the initial levels. No change was observed in the other two cases. No reticulocytosis was observed in any case.

Experimental evidence suggests that androgenic hormones may influence blood formation. Vollmer and Gordon (1941) noted an increase in the red-cell count after testosterone was given in rats, and Finkelstein *et al.* (1944) found that testosterone accelerated the rate of recovery from post-haemorrhagic anaemia in male rats. Korenchevsky and Hall (1945) also reported that androgens increased the red-cell count and haemoglobin in both normal and castrated male rats; Crafts (1946), however, found that, although testosterone prevented a fall in the red-cell count in hypophysectomized rats, the haemoglobin level fell.

There are few reports in the literature of the effects of androgens on the blood in cases of human hypopituitarism, and the evidence of these is inconclusive. Williams and Whittenberger (1942), using a blunderbuss therapy which included testosterone, reported a slight increase in both the red-cell count and the haemoglobin. Daughaday *et al.* (1948) found varying effects from testosterone in their cases. Thus, in their Case H. O. there was little change in cells or haemoglobin after one month's treatment with testosterone, but at the end of seven months there was a rise of nearly 30% in the red-cell count and 10% in the haemoglobin. These changes were accompanied by a small increase in the M.C.V. A similar response was recorded in their Case H. O. N. after several months' treatment, but in Cases T. R. and M. T. no significant change in cells or haemoglobin occurred.

In the present series the results following testosterone therapy are variable, and this, together with the evidence in the literature, suggests that the androgenic hormones have no specific effect on the anaemia of human hypopituitarism.

Iron

Iron, both orally and intravenously, was tried on Cases 2, 4, and 10, all of whom subsequently had other treatment. No significant change in either the red-cell count or haemoglobin was observed. The details are given in Table IV.

TABLE IV

Case No.	Before Treatment		After Treatment (1,000 mg. Ferrivenin)	
	R.B.C. mil./c.mm.	Hb g./100 ml.	R.B.C. mil./c.mm.	Hb g./100 ml.
2	3·2	9·6	3·4	9·4
4	3·5	9·4	3·6	9·3
10	4·2	12·0	4·1	12·0

Beneficial effects from the administration of iron in these cases have rarely been reported, although Jersild and Iversen (1943) did report one case in which iron salts appeared to have a beneficial effect on the anaemia. Crafts (1946) has also shown that iron does not prevent the development of anaemia in hypophysectomized rats, although the rate of development was slowed; he also demonstrated that the haemoglobin levels continued to fall in these animals, although iron was being administered continuously.

Liver

Normoblastic marrow was obtained in all these cases, and therefore the anaemia was considered to be unresponsive to liver, folic acid, or vitamin B_{12}, which are of such value in treating the megaloblastic anaemias.

Cortisone and A.C.T.H.

When supplies of cortisone and A.C.T.H. became available for experimental treatment, the opportunity was taken to treat two cases of hypopituitarism with cortisone and two with A.C.T.H.

Cortisone.—Case 2 had previously been treated with iron, progesterone, testosterone, and chorionic gonadotrophin. No treatment of any sort had been given for eight months before cortisone therapy; the second patient (Case 8), who was treated with cortisone, had also been treated with testosterone before she came under observation, but had had no treatment for five months before the beginning of cortisone therapy. Cortisone acetate, 100 mg. daily intramuscularly, was given to Case 2 for 20 days, when she refused to have any further injections. She was observed for one month before treatment was begun, during which time frequent blood examinations were made. She returned to hospital 44 days after the cessation of treatment, when her condition had relapsed to what it had been before treatment was started. It was possible to treat Case 8 for only 11 days before the supplies of cortisone were exhausted. The effects of cortisone treatment are shown in Table V. In

TABLE V

Case No.	Hb g./100 ml.	R.B.C. mil./c.mm.	M.C.V. μ^3	M.C.H.C. g./100 ml.	Retics. %	Treatment Day
2	9·5	3·2	100	30	0·1	Before treatment
	9·4	3·5	91	30	1·7	7
	10·8	3·9	90	31	3·6	14
	10·5	3·8	90	31		16
8	11·7	4·1	90	32	0·02	Before treatment
	12·1	4·1	90	33	0·02	7
	12·5	4·0	90	33		12

Case 2 cortisone caused an improvement in the red-cell count and haemoglobin, produced a reticulocytosis, and caused a fall in the M.C.V.; in Case 8, although the duration of treatment was limited to 11 days, there was a slight increase in the haemoglobin concentration.

A.C.T.H.—The effects of A.C.T.H. on the blood in two cases are shown in Table VI; the dose given was 75 mg. daily in three injections. Case 3 had previously been treated with thyroid but had had no treatment for two years prior to receiving A.C.T.H.; Case 10 had also been treated with testosterone and iron, but had had no treatment for several months before having A.C.T.H. Unfortu-

TABLE VI

Case No.	Hb g./100 ml.	R.B.C. mil./c.mm.	M.C.V. μ^3	M.C.H.C. %	Retics. %	Treatment Day
10	12·0 11·8	4·2 4·4	88	32	0·1	Before treatment 6
3	9·7 9·7	3·3 3·4	109 109	27 27		14

nately, treatment in Case 10 had to be interrupted owing to the development of a cerebrovascular crisis after 10 days; treatment in Case 3 was continued for 15 days.

Hench *et al.* (1950), reviewing the effects of cortisone and A.C.T.H. in rheumatoid arthritis, noted that the concentration of haemoglobin and also the red blood count improved. Moreover, in Cushing's syndrome, in which there is an increased secretion of the gluco-corticoid hormones of the adrenal cortex, a polycythaemia is constantly found. The prompt response in Case 2 of both the haemoglobin and the red-cell count, and the presence of a reticulocytosis, suggest that cortisone may be capable of curing the anaemia of hypopituitarism. In view of this improvement it was particularly unfortunate that the patient terminated treatment prematurely. The response of the haemoglobin in Case 8 was again suggestive of the potency of cortisone in relieving the anaemia: the duration of treatment in this case is unfortunately too short to allow conclusions to be drawn.

The response of both the cases in which A.C.T.H. was given was disappointing; in neither case, however, was it possible to continue the administration for a very long time, and little change was observed clinically. The occurrence of cerebrovascular episodes in these patients makes it necessary to proceed cautiously with this substance, and in future it might be better to give small doses for a prolonged time.

Summary

Two types of anaemia are found in hypopituitarism—macrocytic hypochromic and normocytic hypochromic. The anaemia is usually of moderate severity.

The response to treatment with thyroid, testosterone, and iron is unsatisfactory, but cortisone seems to produce a prompt increase in the red-cell count and the haemoglobin concentration.

The cortisone and A.C.T.H. used in this work were a gift from Merck and Co. through the Medical Research Council. These substances were made available for this work through Professor H. L. Sheehan, to whom I am also indebted for much helpful advice.

REFERENCES

Balen, G. F. van (1939). *Acta med. scand.*, **101**, 433.
Bloom, A., and Bryson, C. C. (1948). *British Medical Journal*, **2**, 75.
Boller, R., and Goedel, A. (1935). *Wien. Arch. inn. Med.*, **27**, 41.
Caughey, J. E. (1946). *N.Z. med. J.*, **45**, 485.
Crafts, R. C. (1946). *Amer. J. Anat.*, **79**, 267.
Darley, W., Gordon, R. W., and Neubuerger, K. T. (1944). *Ann. intern. Med.*, **21**, 890.
Daughaday, W. H., Williams, R. H., and Daland, G. A. (1948). *Blood*, **3**, 1342.
Finkelstein, G., Gordon, A. S., and Charipper, H. A. (1944). *Endocrinology*, **35**, 267.
Fraser, R., and Smith, P. H. (1941). *Quart. J. Med.*, **10**, 297.
Hench, P. S., Slocumb, C. H., Polley, H. F., and Kendall, E. C. (1950). *J. Amer. med Ass.*, **144**, 1327.
Hird, A. J. (1949). *British Medical Journal*, **2**, 1506.
Jersild, T., and Iversen, K. (1943). *Acta med. scand.*, **116**, 58.
Korenchevsky, V., and Hall, K. (1945). *J. Endocrinol.*, **4**, 103.
de Langen, C. D. (1937). *Ned. Tijdschr. Geneesk.*, **81**, 2896.
Mallory, T. B. (1940). *New Engl. J. Med.*, **222**, 766.
Means, J. H., Hertz, S., and Lerman, J. (1940). *Trans. Ass. Amer. Phys.*, **55**, 32.
Pijper, A. (1919). *Med. J. S. Afr.*, **14**, 472.
—— (1947). *J. Lab. clin. Med.*, **32**, 857.
Price-Jones, C. (1910). *British Medical Journal*, **2**, 1418.
—— Vaughan, J. M., and Goddard, H. M. (1935). *J. Path. Bact.*, **40**, 503.
Robertson, J. S. (1945). *Med. J. Aust.*, **2**, 245.
Sheehan, H. L., and Summers, V. K. (1949). *Quart. J. Med.*, **18**, 319.
Vollmer, E. P., and Gordon, A. S. (1941). *Endocrinology*, **29**, 828.
Williams, R. H., and Whittenberger, J. L. (1942). *J. clin. Endocrinol.*, **2**, 539.
Wintrobe, M. M. (1946). *Clinical Haematology*, 2nd ed. Kimpton, London.
Witts, L. J. (1932). *Lancet*, **1**, 549.

A SURVEY OF PULMONARY EMBOLISM IN A GENERAL HOSPITAL

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A careful watch for pulmonary embolism in all departments of a general hospital combined with the free use of radiography showed thrombo-embolic disease of the lung to be the commonest of all serious acute pulmonary diseases. The radiological appearances having been discussed elsewhere (Short, 1951), the object of this communication is to present the clinical aspects of the condition and to stress its frequency.

Pulmonary embolism or pulmonary infarction was diagnosed in 113 patients admitted to Southmead General Hospital during the two and a half years ending March 31, 1950, and seven cases were seen elsewhere by me during the same period. I examined 85 of the 120 cases personally. The remainder were either rapidly fatal cases, or cases in which the diagnosis was not made before death or discharge from hospital. Necropsy revealed a certain number of unsuspected infarcts, and eight cases were diagnosed in retrospect by looking up the notes of all patients from the surgical and obstetrical wards who had chest radiographs taken post-operatively or in the puerperium. Besides the 120 definite cases presented here, a further 30 were seen in which the diagnosis of pulmonary infarction seemed probable but which are omitted because the evidence was inadequate or because it was impossible to exclude an alternative diagnosis.

Incidence

Table I analyses the cases according to the underlying disease. One-quarter were surgical (post-operative), one-sixth obstetrical, and the remainder (58%) medical. Of the medical cases, four-fifths were suffering from heart disease.

TABLE I.—*Analysis of Cases According to Underlying Disease*

	No.	Pulmonary Infarction	Pulmonary Embolism	Death	Necropsy
Medical ..	70	65	6*	45	41
Surgical ..	30	22	8	10	9
Obstetrical ..	20	19	2*	2	2
Total ..	120	106	16	57	52

* In two instances, pulmonary infarction was followed by massive pulmonary embolism.

Pulmonary embolism or infarction was diagnosed in 2.5% of all medical cases, 0.5% of all surgical cases, and 0.17% of all obstetrical cases. The incidence of pulmonary thrombo-embolism exceeded that of all other serious acute pulmonary diseases during this period, including lobar pneumonia (Table II).

TABLE II.—*Hospital Admissions over Two and a Half Years of the Major Pulmonary Diseases (Excluding Tuberculosis)*

Disease	No.
Primary pleural effusion	33
Primary carcinoma of lung	50
Lobar pneumonia	100*
Pulmonary embolism and infarction	113

* This figure from the hospital records may include some cases of bronchopneumonia and virus pneumonitis; it is probably too high.

In contrast with the reports of Farr and Spiegel (1929), de Takats et al. (1940), and Oschner (1945), and in agreement with the large review of Pilcher (1937), no seasonal variation was evident.

Medical Cases

Although pulmonary embolism is often more dramatic in surgical and obstetrical patients, it is more frequent in the medical wards and particularly in patients with heart disease (White, 1940; Carlotti *et al.*, 1947).

Cases With Heart Disease

In addition to the 54 cases with heart disease admitted to the medical wards, two were admitted to the obstetrical wards on account of pregnancy and one to a surgical ward with retention of urine. Of these 57 cases, rheumatic heart disease accounted for a little less than half, and hypertensive and coronary disease for just under a quarter each.

Approximately 10% of all cases of heart disease admitted to hospital during this period were complicated by pulmonary embolism. The incidence was highest in rheumatic and coronary disease (15% in both groups) and lowest in hypertensive heart disease (5.6%). In half the cases of coronary disease, pulmonary infarction followed an episode of myocardial infarction. In four cases the interval between the two events was less than five days, and in none was it longer than a fortnight.

Pulmonary Congestion.—Judged by the presence of rales and radiographic evidence of marked hilar engorgement, pulmonary congestion was estimated to be severe in 76% of the cases with heart disease at the time of examination (Table III). A similar degree of pulmonary congestion was seen in only 4% of cases without heart disease, and in 37% it was considered to be absent altogether.

TABLE III.—*Degree of Pulmonary Congestion in the 94 Cases in Which a Radiographic Examination was Made*

	No.	Severe	Moderate	Absent
With heart disease	46	35	10	1
Without heart disease ..	48	2	28	18
Total ..	94	37	38	19

Arrhythmia.—Established auricular fibrillation was present prior to pulmonary embolism in 15 cases, a paroxysm of auricular fibrillation in 6, and auricular flutter in 2. The remaining 60% were in normal rhythm.

Thrombosis of Veins.—There were signs of deep femoral thrombosis in five cases, saphenous thrombophlebitis in six, and thrombosis of the brachial and cephalic veins in two. In addition, one patient was suffering from gangrene of the leg with presumptive venous thrombosis. In the remaining 43 cases there was no clinical evidence of venous thrombosis, though bilateral oedema of the legs due to congestive heart failure was present in 26 of them.

Recurrent Embolism.—There were several instances in which repeated pulmonary embolism led to a fatal issue. The following case history of a man aged 26 with rheumatic mitral stenosis illustrates this feature.

> Haemoptysis, followed by a left-sided haemorrhagic pleural effusion, led to the diagnosis of the first pulmonary infarct in November, 1947. The second occurred in the following February and precipitated the development of congestive failure. The third episode did not occur until February, 1949, when left saphenous thrombophlebitis was followed by an attack of right-sided pleuritic pain. There was further infarction of the right lung in May of the same year, and in September he was admitted for the last time with three fresh infarcts.

Mortality.—Of the 57 cases of heart disease complicated by pulmonary infarction, 36 were fatal. In 14 cases death was a direct result of the pulmonary complication, and in 13 cases pulmonary infarction was an important factor in determining a fatal issue. The nine remaining deaths were due to cardiac failure, pulmonary infarction being incidental.

Cases Without Heart Disease

This group of 16 cases falls into three subgroups. The first consists of seven patients with long-standing saphenous varicosities, thrombophlebitis, and, in several cases, crural ulceration. The second is composed of six elderly patients (aged 59 to 70) suffering from a variety of chronic illnesses involving prolonged recumbency. The third consists of three patients, previously quite healthy, in whom pulmonary embolism occurred without obvious cause. The first and last of these subgroups require brief comment.

Whereas pulmonary embolism is often regarded as an uncommon complication of saphenous thrombophlebitis, the occurrence of seven cases in two and a half years suggests that its importance has been underestimated. Three of the cases were fatal—one from massive embolism, another from extensive infarction, and a third from chronic cor pulmonale following repeated embolism. In these cases the emboli arise not from the saphenous system but from the deep veins which become invaded by extension through the saphenous or popliteal openings (Wright, 1948), or which may have been the seat of previous thrombosis (Bauer, 1946).

The fact that pulmonary embolism may occur without warning in apparently healthy persons is emphasized by the three cases admitted to hospital with a diagnosis of pneumonia which had subsequently to be changed to pulmonary embolism. The history of the one fatal case will serve as a typical example.

> A woman aged 49 gave a history of 13 days' left-sided pleuritic pain, cough, and fever. Sulphonamides had been administered for four days without benefit. Examination revealed a pleural rub at the left base with signs of consolidation. There was no history or evidence of thrombosis in the veins of the legs. Radiography showed a shadow at the left base and another small one at the right base. She made good progress, though there was no dramatic response to penicillin. A second radiograph, taken 11 days after admission, showed the left base virtually clear, though the diaphragm on that side was raised and there was also a small pleural adhesion at the right base. The following day the patient had a massive pulmonary embolism and died suddenly. At necropsy, the embolus was found in the main pulmonary artery and there was thrombus in the right popliteal vein.

Such cases, although not often fatal, are probably much commoner than is realized. In 1943 Homans reported 11 similar instances of thrombus developing silently in the deep veins of the leg in healthy persons whose first symptoms were those of pulmonary embolism or infarction.

Surgical Cases

Pulmonary embolism was diagnosed in 30 surgical cases, being responsible for death in eight. Adults of all ages were affected, but massive embolism was much more frequent in the elderly. Although only 27% of the patients were over 60, 62.5% of the instances of massive embolism were in this age group. Only one patient had heart disease. Eight had mild or moderate hypertension, but these showed no evidence of heart failure at the time of examination.

TABLE IV.—*Surgical Cases—Operations Performed*

Abdominal section (including partial gastrectomy 5, appendicectomy 5, hysterectomy 3)	20
Genito-urinary (including prostatectomy 2, suprapubic cystostomy 2)	5
Inguinal hernia	3
Miscellaneous:	
Bilateral compound fracture of tibia and fibula ..	1
Trendelenburg operation for varicose veins	1

Note.—In cases in which two operations were performed the major one is named. In three cases the appendix was removed at the close of the primary operation. In one case a herniotomy was performed after abdominal section. None of the five appendicectomies was straightforward, a gangrenous organ or an abscess being found on each occasion.

Type of Operation.—A negligible amount of cranial and thoracic surgery was performed at the Southmead General Hospital during this period, hence the finding (Table IV) that all the operations in this series were below the diaphragm is of no significance. It should also be mentioned that most of the gynaecological and fracture surgery was undertaken elsewhere. It has often been noted that cases in which infection is present and those in which the operation is long and difficult appear to be particular candidates for pulmonary embolism, and the present small series may be regarded as supporting these observations.

Thrombosis of Veins.—Thrombosis of the deep or superficial veins of the leg could be demonstrated in 50% of cases. There was clinical evidence of deep thrombosis in eight and of superficial thrombosis in three more. In four cases necropsy revealed thrombosis in the veins of the soleus muscle which had not been suspected during life. In two cases emboli appeared to arise from a leg in which saphenous phlebitis followed the use of this vein for transfusion.

Time of Embolism.—The majority of emboli occurred during the first and second post-operative weeks. In four cases there was a close relationship to first risings, as in the following examples:

A man aged 75 underwent retropubic prostatectomy. Three days later he got out of bed for the first time since the operation and had a fatal collapse 10 minutes later.

A man aged 74 underwent retropubic prostatectomy but remained in bed 12 days. On the twelfth day the house-surgeon urged him to start sitting out. Much against his will, he did so. After one and a half hours he complained of feeling faint and was helped back to bed, where he collapsed and died quickly.

In both instances the pulmonary artery was found to contain a long coiled thrombus which had originated in the lower limb.

Both mechanical and humoral factors may be operative in these cases. Chapman and Linton (1945) have shown that the act of straining at stool gives rise to violent fluctuations in venous pressure and flow in which any thrombus that may be present in the femoral veins tends to be dislodged. A similar mechanism probably comes into play in the effort of getting out of bed. Frequently the two events are combined, the first day out of bed being also the occasion of the first visit to the lavatory, though this was not specifically noted in the cases described above.

Macfarlane and Biggs (1946) have shown that fibrinolysin is activated by fear. This factor may be important (by causing detachment of thrombus) in those cases in which a patient is urged to sit out of bed against his inclinations and perhaps with considerable apprehension; or even if there is a dread of painful defaecation.

Obstetrical Cases

Considering the large number of deliveries, normal and abnormal, conducted in hospital, an incidence of pulmonary embolism of 0.17% is not high, a fact which is probably related to the low average age of the patients. Nevertheless there were two fatal cases in two and a half years, and a similar outcome was avoided in several others by only a small margin. The two factors which appeared to predispose to pulmonary embolism were age and any complication of pregnancy, delivery, or the puerperium. Of the cases, 55% were over 30, although only 30% of the women admitted to the obstetrical wards were in this age group. In other words, the incidence of pulmonary embolism in those under 30 was 1.1 per 1,000, whereas in those over 30 it was 3.1 per 1,000.

With one exception, pulmonary embolism was never seen in the absence of clinically obvious femoral venous thrombosis or some complication of pregnancy or delivery (Table V).

TABLE V.—*Analysis of Obstetrical Cases*

Case	Age	Femoral Thrombosis	Complication
6	37	+	Caesarean section
18	37	+	" "
38	31	+	
50	37		Toxaemia, hysterotomy
52	27	+	
57	24	+	
61	24	+	
62	20		Forceps delivery
65	33		Toxaemia, hysterotomy
71	35	+	
78	22		Peritonitis
79	32		Manual removal of placenta
82	42	+	
83	19		Evacuation of uterus
84	28		Rheumatic heart disease
88	35	+	
89	26		
97	20		Toxaemia
111	45		Rheumatic heart disease, caesarean section
147	39	+	Toxaemia, hysterotomy

Necropsy

Of the 57 deaths, 30 were a direct result of pulmonary embolism or infarction. A necropsy was performed in 52 cases, the presence of a pulmonary embolus or infarct being confirmed in all except four. In three of these serial radiography indicated that the infarct had resolved before death. In the fourth—a case of mitral stenosis and auricular fibrillation with good clinical and radiological evidence of two pulmonary infarcts between two and five months before death—the appearances were distorted by brown induration and pulmonary collapse secondary to long-standing pleural effusion.

In over half the necropsies there was evidence of more than one pulmonary infarct. Taking all evidence—clinical, radiological, and post-mortem—together, 52% of the 106 patients with pulmonary infarction gave evidence of two or more infarcts. Pleural effusion related to the pulmonary infarction was found in 11 cases, being blood-stained in five.

Origin.—In 29 of the necropsies a thorough search was made for the site of origin of the embolus. (This may necessitate dissection of the calf muscles and foot, which was prevented in some instances by restrictions.) Of these 29 cases, thrombus was found in the veins of the lower limb in 83%, in the heart in 17%, and elsewhere in 7% (Table VI). In two cases two potential origins were found. It is noteworthy that thrombus was found in the right heart chambers in only 5 of the 36 cases of heart disease—in each of which there had been long-standing auricular fibrillation—and in one of these an alternative origin was present in the femoral veins.

In 13 cases necropsy revealed thrombus in the femoral veins which had not been suspected during life. Three patients with chronic congestive failure were found to have thrombus in either the femoral or the profunda femoris vein. Thrombus was also found in the femoral vein in two cases of heart disease in which oedema of the legs had never been detected.

TABLE VI.—*Source of Embolus Discovered at Necropsy—29 Cases*

	No.	Leg	Heart	Elsewhere
Medical	22	18	5	1
Surgical	5	5	—	—
Obstetrical	2	1	—	1
Total ..	29	24	5	2

Note.—In two cases two potential origins were discovered.

Clinical Picture of Pulmonary Infarction

The non-resident medical staff see few cases of pulmonary embolism without infarction. Massive embolism occurs most often in the surgical and obstetrical wards, and the crisis is usually past before outside help can be obtained. Smaller emboli, on the other hand, are often overlooked. The patient may complain of transitory breathlessness or

faintness or momentary tightness in the chest. Physical examination generally reveals nothing abnormal, and radiography, too, is frequently negative, though an area of abnormal translucency may be found if sought for carefully (Westermark, 1938). A minority of cases show an abnormal electrocardiogram.

Signs in the Chest

The physical signs in the chest in pulmonary infarction depend on three main factors which may be found either singly or in combination—namely, consolidation, pleurisy, and elevation of the diaphragm.

Shortly after infarction it was generally noted that the respiratory rate was raised and the movements of the chest were restricted. Auscultation sometimes revealed little abnormal. The commonest findings during the first 36 hours were diminished air entry and a few rales; less commonly there was a pleural rub. Later the percussion note might become moderately or markedly impaired and bronchial breathing be heard. In some cases there was tubular breathing without rales. Since the lower lobes are most often affected, the signs were most commonly found at the bases, posteriorly and laterally. Marked symptoms were sometimes produced by small infarcts with very localized signs.

Signs of pleural effusion were present in one-sixth of the cases, though radiology demonstrated the presence of hydrothorax in almost twice this number. In the absence of heart disease the amount of fluid was rarely great. Where an effusion of moderate size covered an area of infarction, the stony dullness to percussion associated with bronchial breathing was sometimes very striking.

Significant elevation of the diaphragm was demonstrated radiologically in 35% of cases. It was found in over 50% of cases without heart disease and was sometimes extreme. Clinically, this gave rise on the left side to a tympanitic percussion note at a higher level than usual, and in one case gastric resonance was found as high as the fourth intercostal space in the mid-axillary line. Marked elevation of the right dome produced signs simulating pleural effusion, and in three cases, in which the elevation was associated with pleural adhesion, it actually led to attempted paracentesis thoracis.

A radiographic examination is undoubtedly the most valuable aid to the bedside diagnosis of pulmonary infarction. A suggestive or confirmatory picture may be expected at some time in the course of the disease in almost every case (Short, 1951).

Tachycardia and Arrhythmia

Some degree of tachycardia is the rule in pulmonary infarction, and rates as high as 140 a minute are not uncommon. In the present series a regular rate exceeding 120 a minute was found in 19 cases (Table VII). In 18 the mechanism was simple sinus tachycardia, but in one case the electrocardiogram showed ventricular tachycardia. This latter patient had a myocarditis of uncertain aetiology and died within a fortnight.

TABLE VII.—*Tachycardia and Arrhythmia in Pulmonary Infarction*

	No.	Pre-existing Infarction				Following Infarction		
		A.F.	A.F.(P.)	Fl.	H.B.	S.T.	P.T.	A.F.(P.)
Medical ..	65	15	6*	2	—	11	1	3
Surgical ..	22	—	—	—	1	4	—	1
Obstetrical	19	—	—	—	—	3	—	1
Total ..	106	15	6*	2	1	18	1	5

A.F. = Auricular fibrillation. A.F.(P.) = Auricular fibrillation (paroxysmal). Fl. = Auricular flutter. H.B. = Heart-block (auriculo-ventricular). S.T. = Sinus tachycardia (over 120 a minute). P.T. = Paroxysmal tachycardia (ventricular).

* In three cases it was impossible to be certain whether the arrhythmia preceded or followed infarction.

Occasionally pulmonary embolism induces a paroxysm of auricular fibrillation. When auricular fibrillation is found in a case seen for the first time after pulmonary embolism it is often impossible to tell whether the arrhythmia was present beforehand or not. Usually it may be assumed to have preceded the embolism; the reverse is much less common. The present series, however, includes five cases in which there was good evidence that auricular fibrillation was induced by pulmonary embolism. Four were suffering from heart disease; the history of the fifth, a surgical case, was as follows:

> A man, aged 60 and hitherto healthy, was sent to a cardiologist on account of attacks of epigastric pain. No evidence of heart disease was found, though his blood pressure was 240/110. There was no cardiac enlargement, and the electrocardiogram was normal apart from occasional auricular extrasystoles. A barium-meal examination revealed a large gastric ulcer. Partial gastrectomy was performed in January 26, and seven days later he was observed to have thrombophlebitis of the right long saphenous vein, which had been used for transfusion during the operation. The same day, on his way back from the lavatory, he collapsed with pain in the chest and a feeling of faintness. The following day he expectorated some blood and complained of left-sided pleuritic pain. Diminished air entry and a few rales were audible at the left base, and, later, radiography showed a shadow in the left costophrenic angle. When first seen on the day of the pulmonary embolism the pulse was regular at 120 a minute. Next day the pulse was irregular and the electrocardiogram confirmed auricular fibrillation. The rhythm reverted to normal after digitalization and was still regular when the patient was last seen two years later.

Unexplained tachycardia or rapid auricular fibrillation not controlled by adequate doses of digitalis in a patient with heart disease should suggest three possible complications—namely, active carditis, thyrotoxicosis, and pulmonary infarction. The last-named is often a stealthy process in the presence of cardiac failure, and is easily overlooked.

Haemoptysis

If pulmonary infarction is not diagnosed in the absence of haemoptysis most cases will be missed, for this symptom was present in less than 40% of the total and in only 17% of those without heart disease. The amount of blood expectorated was usually small, though occasionally it was considerable and was continued for as long as a week.

Haemoptysis is a well-recognized symptom of heart disease, apart from pulmonary infarction, in patients with mitral stenosis or left ventricular failure. Nevertheless, persistent or recurrent haemoptysis in a patient with heart disease should always suggest pulmonary infarction.

Pleurisy

Next to haemoptysis, pleuritic pain is perhaps the most dramatic symptom of pulmonary infarction. Ninety per cent. of the surgical and obstetrical patients complained of it, though a pleural rub was heard in only a quarter of these (Table VIII). One-sixth of the cases developed signs of hydrothorax. In the majority the amount of fluid was small, rarely exceeding half a litre.

TABLE VIII.—*Incidence of Pleurisy in Pulmonary Infarction*

	No.	Pleuritic Pain	Pleural Rub	Pleural Effusion
Medical	65	30	14	15
Surgical	22	20	6	4
Obstetrical ..	19	17	4	3
Total ..	106	67	24	22

Note.—This table excludes cases with hydrothorax due to cardiac failure and those with small amounts of fluid not detected clinically.

In patients with heart disease pleuritic pain was rarer and effusion more common. Several of these patients presented with a large unilateral effusion. In such cases the fluid often showed a tendency to persist for months despite a good general response to digitalis and mersalyl.

There was an opportunity of inspecting the fluid, either by paracentesis or at necropsy, in 17 cases. It was haemorrhagic in eight. It is sometimes taught that an effusion resulting from pulmonary infarction is inevitably haemorrhagic, but in corroboration of the present findings it may be recalled that Spain and Moses (1946) found macroscopic blood in only 13 out of 47 effusions.

In one case an empyema resulted from secondary infection of an infarct followed by rupture of the abscess into the pleural cavity. In the remaining eight cases a yellow serous fluid was found. One specimen submitted for microscopy and culture was reported as sterile and containing an occasional lymphocyte. Such a fluid could easily be regarded as tuberculous in a case presenting without a characteristic history. A routine test for bile pigments was unfortunately not made. It has been suggested (Krause, 1945) that their presence in an effusion (presumably in the absence of jaundice) is diagnostic of pulmonary infarction.

Jaundice

Jaundice was observed in almost a third of the cases of heart disease complicated by pulmonary infarction. Half the patients were suffering from rheumatic heart disease. It was only once seen in a case of pulmonary infarction without heart disease, and in this instance the patient was found to have a chronic haemolytic anaemia.

Clinically, the depth of jaundice varied from a slight tinge to a deep yellow. Bile was present in the urine in one-third of the cases in which it was tested for. The serum bilirubin was estimated in 12 cases. In 11 the level was above 2 mg./100 ml., and in one it was 5 mg./100 ml. A raised serum bilirubin is probably present in most cases of severe passive congestion of the liver apart from pulmonary infarction (Kugel and Lichtman, 1933). Nevertheless, clinical jaundice is most frequently associated with pulmonary infarction.

Thirteen cases came to necropsy: cardiac cirrhosis of the liver was present in two, evidence of severe chronic venous congestion in seven, evidence of mild chronic venous congestion in one, and the liver appeared macroscopically normal in three. In six cases the volume of lung infarcted amounted to one lobe or more, in the remainder to half a lobe or less, and in one instance to no more than one-eighth of a lobe. In every case there was evidence of severe and long-standing pulmonary congestion.

Jaundice in heart disease complicated by pulmonary infarction has been considered to be mainly haemolytic owing to the destruction of red cells in the infarct. Kugel and Lichtman believed that infection was also an important factor in some cases. They explained its action partly on the basis of an enhanced activity of the reticulo-endothelial system causing an acceleration in the absorption of bilirubin from the infarct, and partly on a toxic action on the liver. Infection did not appear to play an important part in the aetiology of jaundice in the present series except in a single instance. The case with the smallest infarct and a liver which appeared normal was complicated by extensive lobar pneumonia.

During the period of two and a half years covered by this study transient jaundice was seen in three women with heart disease (not included in this series) in whom careful clinical and radiological examination revealed no definite evidence of pulmonary infarction. Two of these had mitral stenosis with normal rhythm, one of them being in congestive failure. The third had hypertensive heart disease, thyrotoxicosis, and auricular fibrillation with severe congestive failure, and the jaundice was at one time quite marked. In none of these cases was there any clinical evidence of disease of the biliary tract or gross hepatic pathology.

Although the development of jaundice in a case of heart disease should strongly suggest pulmonary infarction, such a lesion is not invariably present. Sherlock (1945) has shown that where the pressure in the great veins is markedly raised the resulting high pressure in the hepatic sinusoids may produce a mechanical blockage of the bile canaliculi with consequent obstructive jaundice. In the third case, mentioned above, hepatic damage due to thyrotoxicosis (Youmans and Warfield, 1926) may have played a part.

Treatment

Provided there was no contraindication, all cases of deep femoral thrombosis were treated with dicoumarol, a low prothrombin index being maintained until the patient was active. To obtain an immediate anticoagulant effect heparin was usually given for the first 48 hours with the dicoumarol. No case so treated developed pulmonary embolism and no serious bleeding was encountered.

It was intended to treat similarly all cases of pulmonary embolism in which an early diagnosis was made. Actually, one-third of the cases in this series received a course of anticoagulant therapy. Although the number of treated cases and controls was insufficient for a statistical analysis, the beneficial effect was impressive. Purpura and haematuria were encountered in one case and purpura alone in another. Dicoumarol must be blamed for one death. A patient who had undergone partial gastrectomy developed pulmonary embolism on the seventh post-operative day. Dicoumarol therapy was begun at once, and after four days the prothrombin index was returned as 60%. He died suddenly the following day, and at necropsy 3 litres of blood was found in the peritoneal cavity. Greater familiarity with dicoumarol and the difficulties of the prothrombin estimation eliminated haemorrhagic complications entirely during the final year.

Femoral vein ligation was considered in three patients in whom repeated pulmonary embolism occurred over a period of several months, but was never actually performed. Two of them, who were suffering from advanced mitral disease, died. The third, a post-operative case, recovered on a prolonged course of dicoumarol. In retrospect, it is believed that the two cases with mitral stenosis might have been protected from further emboli by long-term dicoumarol therapy (Cosgriff, 1950).

Discussion

Pulmonary embolism accounts for between 5% and 7% of all post-operative and maternal deaths (McCartney, 1945). It is the direct cause of death in a similar proportion of cases of coronary thrombosis (Eppinger and Kennedy, 1938) and probably of rheumatic heart disease also. In addition there are the many deaths, particularly in patients with heart disease, in which pulmonary embolism is an important contributory factor. Furthermore, as other causes of death are being steadily reduced by the advances in surgery, obstetrics, anaesthesia, and post-operative care, the relative importance of pulmonary embolism is increasing. A survey of necropsies carried out at two general hospitals in Bristol between 1913 and 1948 (Short, unpublished) showed that massive pulmonary embolism was the principal cause of death in 4.5 per 1,000 necropsies in the five-year period 1913–17, 8.1 per 1,000 in 1929–33, and 16.8 per 1,000 in 1944–8.

During the past decade it has been increasingly realized that most pulmonary emboli are not massive and fatal, and that they concern physicians as least as much as surgeons and obstetricians. Indeed, the present study suggests that thrombo-embolic disease of the lung may have become the commonest of serious acute pulmonary lesions in general hospital practice.

There is reason to believe that in the surgical and obstetrical wards many pulmonary infarcts are misdiagnosed as pleurisy, pulmonary collapse, or pneumonia. In the medical wards many are overlooked, for the symptoms in patients suffering from cardiac failure are often far from striking. Pleuritic pain is often absent, and the elevation of temperature, pulse, and respiration rates may be slight. Furthermore, several of the symptoms and signs of pulmonary infarction are met with in heart disease in the absence of a focal lung lesion—for example, haemoptysis, basal rales,

and pleural effusion. Even radiography may be unreliable owing to the tendency of pulmonary congestion to obscure the infarct shadow. The diagnosis must continually be borne in mind and should be suggested particularly by the following signs: continuous or recurrent haemoptysis, unexplained tachycardia, jaundice, and a large unilateral effusion which persists or recurs despite a satisfactory general response to therapy.

Pulmonary embolism is common in patients bedridden from any cause, especially where dehydration or anaemia is present. It also occurs in patients with long-standing saphenous thrombophlebitis. Furthermore, it must be considered in the differential diagnosis of pneumonia, for femoral thrombosis is sometimes a silent process and the first symptom may be pulmonary.

Despite the warnings which have been sounded during the past decade, the general attitude towards femoral venous thrombosis and minor pulmonary emboli is still far too complacent. These events are by no means so benign as they are sometimes pictured, and as warnings of possible massive embolism they are of outstanding importance.

Bauer (1946) has declared that femoral thrombosis treated conservatively—that is, without anticoagulants—is followed in almost every case by chronic oedema, in 90% of cases by indurative lesions on the lower leg, and in 80%, sooner or later, by crural ulceration.

Pulmonary infarcts often resolve without serious consequences. Nevertheless, in the present series they accounted directly for the deaths of 15 patients and were an important contributory factor in 13 others. Pulmonary infarction almost led to a fatal issue in five otherwise healthy surgical and obstetrical subjects. One, a patient admitted for a Trendelenburg operation for varicose veins, had to be detained in hospital for four months and undergo a rib resection on account of an empyema which resulted from infection of a pulmonary infarct.

Every thrombo-embolic incident should be regarded as a warning of possible massive embolism. On the basis of collected reports, totalling over 4,000 cases, it has been shown (Cosgriff, 1947) that in the absence of anticoagulant therapy or venous ligation 20% to 30% of all patients with femoral venous thrombosis will develop a pulmonary embolus and 6% to 14% a fatal one. Of cases which have had one pulmonary embolus, 30% will have another and 18% a fatal one.

The importance of watching the legs of all post-operative and puerperal patients and those with recent myocardial infarction is still not appreciated. It is the early signs which are important—a raised skin temperature, local tenderness in the calf, and a positive Homans dorsiflexion sign. It is because this stage is overlooked that pulmonary embolism is regarded as unheralded. The frequency with which thrombus is found in the deep femoral veins (Carlotti *et al.*, 1947) and the relative infrequency with which it is found in the right side of the heart, indicate that even in heart disease most pulmonary emboli arise in the legs.

Post-operative pulmonary infarction is often misdiagnosed as massive collapse, pneumonia, or pleurisy. While this paper was in preparation such a misdiagnosis had a tragic sequel. A patient underwent a nasal operation in another hospital. Eight days later she complained of pleuritic pain in the chest. A radiographic examination was requested and pleurisy was diagnosed. Five days later the patient collapsed and died suddenly from massive pulmonary embolism. The fatality was unexpected but not unheralded. Had the warning been recognized, the fatality might have been averted by anticoagulant therapy. A complaint of pleuritic pain within three weeks of operation or delivery should be regarded as indicating pulmonary infarction until this has been disproved.

There is considerable evidence that anticoagulant therapy reduces the incidence of pulmonary embolism in femoral thrombosis (Cosgriff, 1947) and myocardial infarction (Wright *et al.*, 1948; Tulloch and Gilchrist, 1950) and reduces the risk of further embolism when one has already occurred (Cosgriff, 1947). It has been demonstrated that heparin is capable of dissolving thrombus already formed—at least in experimental myocardial infarction (Solandt *et al.*, 1939)—but the fear that anticoagulants might loosen thrombus present in the femoral veins and so encourage embolism has proved to be unfounded. Where necessary, both heparin and dicoumarol may be given within eight hours of operation (Jorpes, 1946) and within 12 hours of delivery (Leissner, 1941).

In view of the apparent danger of thrombus becoming detached when the patient first gets out of bed after operation, anticoagulant therapy once started should be continued until the patient is active. Indeed, in cases in which the risk of embolism is great—for example, following prostatectomy—it would appear to be reasonable to employ anticoagulant therapy over this danger period even in the absence of other indications.

It is freely admitted that anticoagulants at present available are neither easy to control nor free from danger. They are, nevertheless, both reasonably effective and reasonably safe in experienced hands, and their use until something better is discovered is fully justified.

Although femoral vein ligation was not employed on any case in this series, experience suggests that it may have a small but definite sphere of usefulness in those cases in which repeated embolism occurs despite anticoagulant therapy or in which such therapy is contraindicated.

Summary

Pulmonary thrombo-embolism was diagnosed during a period of 30 months in 120 patients, of whom 113 were in the wards of a general hospital. The incidence of pulmonary thrombo-embolism in this hospital was higher than that of lobar pneumonia. Pulmonary embolism was directly responsible for 30 deaths, and pulmonary infarction was an important contributory factor in 13 more.

Fifty-eight per cent. of the cases were classed as medical, and 80% of these had heart disease. There were three instances (one fatal) of pulmonary embolism appearing without warning in apparently healthy subjects.

Among the 30 surgical cases (8 fatal) were 4 in which pulmonary embolism was precipitated by first rising.

Among the 20 obstetrical cases (2 fatal) pulmonary embolism was nearly three times as common in those over the age of 30 as in those under 30. Pulmonary embolism was only once seen in the absence of obvious femoral thrombosis or some complication of pregnancy or delivery.

Pleuritic pain and haemoptysis are the two most striking symptoms of pulmonary infarction. Pleuritic pain was noted in 65% of all cases and was present in fully 90% of the surgical and obstetrical cases. Haemoptysis was noted in less than 40% of all cases; the incidence falls to 17% if cases with heart disease are excluded.

The physical signs in the chest in pulmonary infarction depend on the presence and degree of three factors—namely, consolidation, pleurisy, and elevation of the diaphragm.

Signs of pleural effusion were present in 20% of cases. The fluid was blood-stained in 8 out of 17 cases in which it was inspected.

Jaundice was observed in almost one-third of the cases of heart disease complicated by pulmonary infarction.

A paroxysm of auricular fibrillation was precipitated by pulmonary infarction in five cases.

In several patients with congestive heart failure the symptoms were slight and the presence of pulmonary infarction was overlooked. In post-operative and puerperal patients the condition was often misdiagnosed as pleurisy, pulmonary collapse, or pneumonia.

The importance of paying serious attention to every case of femoral thrombosis and pulmonary embolism is reiterated, and measures of prophylaxis and therapy are briefly discussed.

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REFERENCES

Bauer, G. (1946). *Lancet*, 1, 447.
Carlotti, J., Hardy, I. B., Linton, R. R., and White, P. D. (1947). *J. Amer. med. Ass.*, 134, 1447.
Chapman, E. M., and Linton, R. R. (1945). Ibid., 129, 196.
Cosgriff, S. W. (1947). *Amer. J. Med.*, 3, 758.
—— (1950). *J. Amer. med. Ass.*, 143, 870.
De Takats, G., Mayne, A., and Petersen, W. F. (1940). *Surgery*, 7, 819.
Eppinger, E. C., and Kennedy, J. A. (1938). *Amer. J. med. Sci.*, 195, 104.
Farr, C. E., and Spiegel, R. (1929). *Ann. Surg.*, 89, 481.
Homans, J. (1943). *New Engl. J. Med.*, 229, 309.
Jorpes, J. E. (1946). *Heparin in the Treatment of Thrombosis*, p. 266. Oxford Univ. Press, London.
Krause, G. R. (1945). *Radiology*, 45, 107.
Kugel, M. A., and Lichtman, S. S. (1933). *Arch. Intern. Med.*, 52, 16.
Leissner, H. (1941). *Acta med. scand.*, 107, 127.
McCartney, J. S. (1945). *Surgery*, 17, 191.
Macfarlane, R. G., and Biggs, R. (1946). *Lancet*, 2, 862.
Oschner, A. (1945). *Surgery*, 17, 240.
Pilcher, R. (1937). *Brit. J. Surg.*, 25, 42.
Sherlock, S. P. V. (1945). *Quart. J. med.*, 14, 222.
Short, D. S. (1951). Ibid., 20, 233.
Solandt, D. Y., Nassim, R., and Best, C. H. (1939). *Lancet*, 2, 592.
Spain, D. M., and Moses, J. B. (1946). *Amer. J. med. Sci.*, 212, 707.
Tulloch, J. A., and Gilchrist, A. R. (1950). *British Medical Journal*, 2, 965.
Westermark, N. (1938). *Acta radiol., Stockh.*, 19, 357.
White, P. D. (1940). *Amer. J. med. Sci.*, 200, 577.
Wright, A. D. (1948). *Proc. roy. Soc. Med.*, 41, 22.
Wright, I. S., Marple, C. D., and Beck, D. F. (1948). *J. Amer. med. Ass.*, 138, 1074.
Youmans, J. B., and Warfield, L. M. (1926). *Arch. intern Med.*, 37, 1.

DEAFNESS WITH USE OF DIHYDROSTREPTOMYCIN IN TUBERCULOUS MENINGITIS

BY

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Attention has recently been drawn to the reduced success and increased deafness resulting from the use of dihydrostreptomycin instead of other forms of streptomycin in the treatment of tuberculous meningitis (Minkenhof, 1950; Biagi, 1951; Cathie and Garrow, 1951; Somner, 1951). My experience in Ayrshire Central Hospital, Irvine, and Belvidere Hospital, Glasgow, seems to confirm the latter finding, although the results, in terms of percentage recovery, have not been adversely affected. Deafness itself, however, is a most perplexing problem, especially since, in my experience, hearing-aids have been of no value to the patients developing it. Lip-reading tuition has been given during their stay in hospital and after dismissal, but this, of course, is a very poor substitute for normal hearing, although it does help them to enter into conversation.

For several months dihydrostreptomycin was suspected as being the cause of increased deafness complicating recovery from tuberculous meningitis—and indeed this was mentioned to representatives of Glaxo Laboratories, who have recently provided supplies of the calcium chloride complex to conduct a controlled investigation on a series of new cases. Unfortunately the introduction of dihydrostreptomycin coincided with an intensification of intrathecal (but not intramuscular) streptomycin therapy, and the possibility that this may have been responsible for the increased incidence of deafness required to be first excluded. Accordingly, when this discovery of increased deafness was made in April of last year, the course of intrathecal streptomycin was reduced to one more closely resembling that previously used, the intramuscular regime being unaltered. It is too early to assess the ultimate results with this course. So far, it does not appear to have affected the recovery rate; but cases of deafness have already occurred. For comparison, this latter course is now being used, the calcium chloride complex being substituted for dihydrostreptomycin. It is hoped to publish later a report on the results.

The courses given and the results obtained are outlined below:

1. Results Prior to Use of Dihydrostreptomycin

The adult course in average cases extended over a period of six months, as follows:

Intramuscular Streptomycin	Intrathecal Streptomycin
2 g. daily in 2 doses for 3 months 1 g. daily for 1 month 1 g. on alternate days for 1 month 1 g. twice weekly for 2 weeks 1 g. weekly for 2 weeks	100 mg. daily for 2 weeks Rest for 1 week 100 mg. daily for 1 week 100 mg. on alternate days for 2 weeks 100 mg. weekly until end of 6 months

Of 26 patients treated, 13 died and 13 survived for periods varying from two to three and a half years. Only one of these became slightly deaf during treatment of a relapse. The deafness has not progressed.

2. Results Using Dihydrostreptomycin

A. Intense Intrathecal Course.—The adult course in average cases extended over a period of six months, as follows:

Intramuscular Dihydrostreptomycin	Intrathecal Dihydrostreptomycin
Exactly as above	100 mg. daily for 2 weeks 100 mg. on alternate days for 8 weeks 100 mg. weekly till end of 6 months

Para-aminosalicylic acid was given concurrently and for a further six months

Of 51 patients treated 17 died and 34 survived for periods ranging from eight months to two years: 20 cases became deaf.

B. Less Intense Intrathecal Course.—The adult course in average cases extended over a period of six months as follows:

Intramuscular Dihydrostreptomycin	Intrathecal Dihydrostreptomycin
Exactly as above	100 mg. daily for 2 weeks 100 mg. on alternate days for 4 weeks 100 mg. weekly till end of 6 months

Para-aminosalicylic acid was given concurrently and for a further six months

Fourteen patients received this course and were observed over a period varying from three and a half to seven months. So far, four have died. Of the survivors two are already becoming deaf.

Modification of Dosage for Children

Intrathecal.—In all series the intrathecal dosage was the same as for adults except in patients under 5 years of age, in whom the maximum intrathecal dose was 50 mg.

Intramuscular.—On the basis that 1 g. was given at each injection to adults, the quantity for children was reckoned as follows:

Aged 15 and over	1 g.
,, 10 to 14	0·75 g.
,, 5 to 9	0·5 g.
,, 0 to 4	10 mg. per lb. (450 g.) body weight

Results

An analysis of the results obtained with these three courses is given in Table I.

TABLE I

Course Used	Total Cases	Alive	Dead	Deafness
1. Streptomycin	26	13 (50%)	13	1
2A. Dihydrostreptomycin	51	34 (67%)	17	20
2B. Dihydrostreptomycin	14	10	4	2

Incidence of Deafness

As the cases in group 2B have been under observation for only three and a half to seven months, it is not yet possible to discuss the incidence of deafness in this series. The following discussion therefore relates only to the 51 patients in the second series, of whom 20 (39.2%) became deaf. Three of these have subsequently died, so that 17 (50%) out of the 34 cases surviving are deaf. Of the 17 patients who died, 5 survived more than three months; thus 39 out of the 51 cases lived more than three months. The incidence of deafness in these 39 cases is 20 (51.3%). This figure is given, since the earliest time at which deafness has been noted is two to three months; 51.3% of patients surviving for this period became deaf.

Of the 20 cases of deafness, 12 were totally deaf, 6 were moderately deaf, and 2 had only slight impairment of hearing. No relationship could be found to the stage of disease and degree of illness when treatment was begun. The usual classification was adopted, and the cases were divided into three categories:—(1) Early: conscious, with only slight meningeal signs and no focal signs, but positive C.S.F. findings. (2) Intermediate: drowsy, with more marked meningeal signs and symptoms, and, possibly, focal signs. (3) Advanced: comatose or semi-comatose, with marked meningeal signs, and focal signs. Table II gives the incidence of deafness in these three groups

TABLE II

Stage of Disease	Total Cases	Dead	Alive	Surviving More Than 3 Months	
				No.	No. Deaf
Early	2	0	2	2	1 (50%)
Intermediate	33	7	26	28	14 (50%)
Advanced	16	10	6	9	5 (55·6%)

In all groups the proportion of deaf cases among those who survived long enough for deafness to occur is the same. Likewise, the incidence of deafness could not be correlated with the presence of miliary tubercles in the lungs or of adult pulmonary tuberculosis, or with other known factors.

The earliest date of onset of deafness was three months from the beginning of treatment, the average time being five months. In a few cases deafness occurred after completion of treatment or during a second course. Although a small proportion of cases developed deafness when their condition was not progressing favourably, most patients appeared either to have fully recovered or to be steadily improving when their hearing began to be impaired. The following brief descriptions of cases treated in Belvidere Hospital, Glasgow, illustrate these findings.

Case Reports

Case 1.—A boy aged 15 was admitted on March 25, 1950, in a comatose state, on the ninth day of illness, with marked meningeal signs. During the first six weeks of treatment progress was slow, but thereafter he improved steadily and by the sixth month was very well, with no meningeal signs, a normal temperature, and C.S.F. returning to normal. During the sixth month he was noticed to be slightly deaf, and in the course of a few weeks the deafness became total. Otherwise he is perfectly well.

Case 2.—A boy aged 9 was admitted on April 17, 1950, with a history of headache and sickness for four days. He was drowsy and listless and had definite meningeal signs. He made a steady uninterrupted recovery, but, though clinically well at the end of six months, the C.S.F. still contained 61 lymphocytes per c.mm. and 100 mg. of protein per 100 ml. After a fortnight without treatment these findings increased and, despite nothing abnormal being found clinically, he was given a further course of treatment. In the fourth month of this course slight deafness developed. In a few weeks this became complete and has remained so. Otherwise he was well, the C.S.F. findings subsequently returning to normal. Deafness is still the only abnormality.

Case 3.—A girl aged 16 was admitted on April 22, 1950, the seventh day of illness, moderately ill with definite meningeal signs, miliary tubercles in the lungs, and choroidal tubercles, but quite bright mentally. She responded to treatment during the first 10 weeks, then her condition remained stationary. In the 14th week of treatment she had a convulsion and went into coma. Retention of urine developed, followed by incontinence and a spastic paresis of her legs, which later became flaccid. The course of dihydrostreptomycin was begun over again and she improved steadily, regaining control of her bladder and power of her legs. After a further 12 weeks, when she was progressing well, she complained of buzzing in her ears and was slightly deaf in the right ear. In six to eight weeks she was totally deaf in both ears but was very well, apart from stiffness of her knees, which required orthopaedic treatment. She is still well but remains totally deaf, although very proficient in lip-reading.

Case 4.—A boy aged 7 was admitted on May 21, 1950, the seventh day of illness. He was only mildly ill, a bit listless, and had slight neck stiffness and very slight left facial palsy. He made an excellent recovery with dihydrostreptomycin and at the end of six months appeared completely well, was up and about, and had no signs of disease and a normal C.S.F. Then he was noticed to be slightly deaf. In a few weeks' time he became totally deaf and has remained so, although perfectly fit otherwise.

Case 5.—A man aged 26 was admitted on October 21, 1950, after three weeks' illness. He was quite bright mentally but had marked meningeal signs. Tuberculin (P.P.D.) was given intrathecally during the first three months of treatment. C.S.F. protein was 460 mg. per 100 ml. on admission. Within a fortnight he had a fully developed spinal block, and intrathecal dihydrostreptomycin was then given by both lumbar and cisternal routes. While tuberculin was being given his condition appeared to be deteriorating and he had many reactions. By the end of the third month deafness was noticed, and in a few weeks was complete. After cessation of tuberculin his condition steadily improved and, apart from his deafness, he made an uninterrupted recovery.

Case 6.—A boy aged 13 was admitted on December 9, 1950, moderately ill, listless, and drowsy, with slight but definite meningeal signs. Tuberculin was given intrathecally for a month, during which his condition remained poor. After discontinuing tuberculin he made steady progress. At the end of the fourth month, when symptoms and signs had abated and his temperature had settled, he was noticed to be slightly deaf. Further recovery was uninterrupted, but deafness has become total.

Case 7.—A girl aged 11 was admitted on December 18, 1950, with a history of a week's illness. On admission she

was semi-comatose and delirious and had fairly marked meningeal signs. In two days she became completely comatose and did not recover full consciousness till after a month, by which time she had a right hemiparesis. Her progress thereafter was slow but steady. During the fourth month of treatment she became deaf: her deafness was moderate and never became complete. A month later her condition deteriorated, spinal block developed, and she died on May 2, 1951.

Case 8.—A man aged 24 was admitted on January 19, 1951, with bilateral pulmonary tuberculosis complicated by tuberculous meningitis. He was irrational and resentful and had marked meningeal signs. Pneumoperitoneum was induced to control the pulmonary tuberculosis, which appears to have healed. His progress was slow, but by the end of the fifth month signs and symptoms had subsided and his temperature had settled. Then he developed slight impairment of hearing, which has now become moderate. Otherwise he is fit, the chest having cleared and the C.S.F. returned to normal.

Conclusions

The results in this series contrast with those outlined by Cathie and Garrow (1951). Their results with dihydrostreptomycin were poorer than those obtained earlier. In the present series the recovery rate with dihydrostreptomycin was 67%, as compared with 50% prior to its use. Other factors, however, have probably contributed to the improvement in results—increasing knowledge and experience of streptomycin, concomitant administration of P.A.S., etc.—and it is doubtful whether any significance can be attached to it. It seems reasonable to deduce, however, that dihydrostreptomycin is at least as effective as other forms of streptomycin in the treatment of tuberculous meningitis.

The series confirms the findings of Cathie and Garrow and other workers in relation to deafness. In contrast with 1 case of deafness out of 13 survivors before the use of dihydrostreptomycin, 50% of survivors became deaf after using this drug. The occurrence of nerve deafness late in the course of treatment in most cases, when the patients appeared to have recovered from the disease and were normal in other respects, suggests that the deafness is unlikely to be caused by the meningitis, but that it is a toxic manifestation—apparently irreversible—of the drug used. It is true that in this series other factors may have contributed to the increased incidence of deafness with dihydrostreptomycin, especially the increased intrathecal dosage of the drug in the second group of cases, but there is enough evidence to warrant caution in using dihydrostreptomycin, and to indicate a controlled investigation of its advantages and disadvantages compared with other forms of streptomycin.

Summary

The results obtained in a series of 26 cases treated with streptomycin are compared with those in a series of 51 cases treated wih dihydrostreptomycin. While the latter showed a 67% recovery rate as compared with 50% in the former, 50% of the survivors in the second series were deaf, whereas only 1 out of 13 survivors in the first series had impairment of hearing.

Some of the features of the deafness are stated, and brief descriptions are given of some illustrative cases.

I wish to thank Dr. M. J. Miller, physician-superintendent, Ayrshire Central Hospital, Irvine, and Dr. T. Archibald and Dr. A. L. K. Rankin, physician-superintendents, Belvidere Hospital, Glasgow, for permission to publish these results and for help given; and Dr. P. McKenzie, deputy physician-superintendent, Belvidere Hospital, for helpful advice. I am also grateful to the nursing staffs of pavilions 8 and 9, Ayrshire Central Hospital, and wards 13 and 23 east, Belvidere Hospital, and to the pharmacy staffs of both hospitals, for their co-operation.

ADDENDUM.—Since this paper was submitted for publication one further case in Group 2A has developed slight deafness, and four more cases in Group 2B—making a total of six cases in this group—have become deaf. These facts confirm the conclusions already reached and stated above, and are in keeping with papers which have appeared more recently. It is hoped to incorporate these further results in a later publication.

REFERENCES

Biagi, R. W. (1951). *British Medical Journal*, 2, 651.
Cathie, I. A. B., and Garrow, D. H. (1951). Ibid., 2, 735.
Minkenhof, J. E. (1950). *Ned. Tijdschr. Geneesk.*, 94, 2129.
Somner, A. R. (1951). *British Medical Journal*, 2, 970.

GROWTH OF BIPARIETAL DIAMETER OF FOETAL HEAD IN THE LAST WEEKS OF PREGNANCY

BY

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Those who favour the early induction of labour for the prevention of cephalo-pelvic disproportion base their practice on the beliefs that during the last weeks of pregnancy the foetal head becomes harder and larger. The second of these two beliefs has been questioned by Josephs (1949), who could not detect radiologically any increase in the biparietal diameter during the last four weeks of pregnancy. This paper is concerned with examining this rather surprising finding.

Methods.—Steel callipers (Fig. 1) fitted with a sprung platform so that measurements could be made under standard conditions of pressure were used to measure the biparietal diameter of infants' heads 48–96 hours after birth.

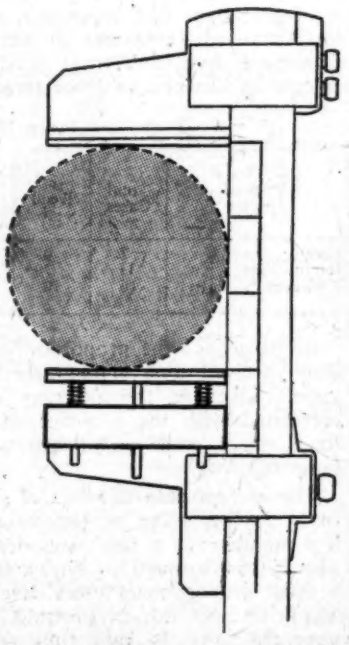

FIG. 1.—Sketch of callipers used in measuring the biparietal diameter of the head, showing the sprung platform.

Results

The individual biparietal diameters of 1,059 infants were plotted against the respective durations of pregnancy as estimated from the first day of the last menstrual period of the mother. A statistical calculation was then made to delimit the area within which two-thirds of all these points fell. This area is represented by the shaded portion of Fig. 2, from which it can be seen that in general the greater the duration of pregnancy the greater the biparietal diameter of the head. In addi-

tion to these 1,059 infants delivered as a result of the spontaneous onset of labour, a further series of measurements of 24 infants delivered after an induced labour during the 35th–38th weeks of pregnancy was made. These results are shown in Fig. 2. It may be noted that 15 out of 24 fall within the shaded area, whilst the mean of these 24 measurements is slightly less than that for babies of a comparable age born spontaneously. The relevance of this finding will become apparent later.

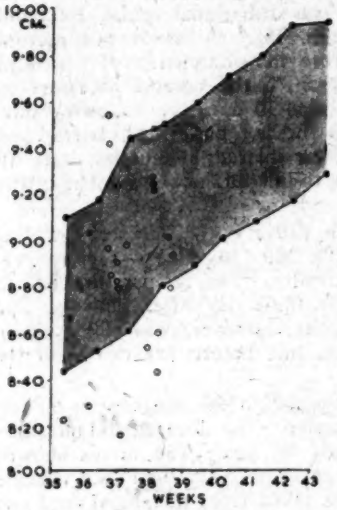

FIG. 2.—Graph showing area delimiting two-thirds of all measured biparietal diameters plotted against estimated duration of pregnancy. The open circles indicate biparietal diameter of heads of infants in which labour was induced before 39 weeks from the last menstrual period.

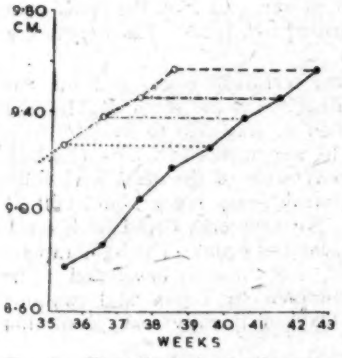

FIG. 3.—Hypothetical growth curves of the biparietal diameter of the foetal head. The continuous line represents the mean biparietal measurements at birth of 1,059 infants; it is in fact the mean line representing growth in this diameter. The broken lines with open circles show how the final mean measurements could be reached even if no growth took place in the last four weeks. This possibility has been excluded (see text).

Discussion

The common-sense conclusion suggested by Fig. 2, that the biparietal diameter continues to grow in the last few weeks of pregnancy, is not inevitable. Each baby was measured only once, and it is possible that had each head been measured a month earlier it would have been the same size as it was when actually measured—that is, the growth curve of Fig. 2 may have been produced as shown in Fig. 3. This is tantamount to saying that four weeks before birth the biparietal diameter of each foetus stopped increasing, no matter whether it was born at 34 or 42 weeks by dates; it also implies that the date of labour was ordained at least four weeks in advance. At its face value this suggestion does not seem likely, but it would reconcile the findings of Josephs with those stated in this paper.

To settle the matter it would be necessary to measure the biparietal diameter of the foetal *head* at 36 weeks and again at 40 weeks. This is not possible, but the line of argument set out in Fig. 3 would imply that pregnancies terminated artificially two to four weeks before the expected date of delivery would produce babies in whom the ratio of biparietal diameter to age was higher than that of babies born naturally. The distribution of the open circles in Fig. 2 clearly indicates that the biparietal diameters of infants born after induction are not systematically different from those of infants born spontaneously at an equivalent period of pregnancy. Thus there is no doubt that the biparietal diameter does increase in the last four weeks of pregnancy. The mean magnitude of this increase is shown in Fig. 4, which is a life-size drawing of the mean circumference of the plane drawn through the bregma, subocciput, and both parietal eminences at 36 and at 40 weeks.

It now remains to inquire why Josephs did not detect the increase of the biparietal diameter of the head which takes place in the last four weeks of pregnancy. The radiological method of measurement of the biparietal diameter assumes that the largest plane at right angles to the longest diameter of the skull is a perfect circle. This assumption is demonstrably false, as may be seen from Fig. 5, which shows the shape of the plane of the biparietal diameter with a circumscribed circle for comparison. The question therefore arises, does any event in the last four weeks of pregnancy give this false assumption a special significance in the measurement of the biparietal diameter which is not present earlier? Clearly one factor which must be taken into account is the descent of the head with the concomitant backward shift into the pelvic cavity. Because the plane of the measurement is not a circle a systematic change in the position of the axis of the foetal head in relation to the pelvis, and therefore

FIG. 5.—Diagram showing the shape of the plane of the biparietal diameter with circumscribed circle.

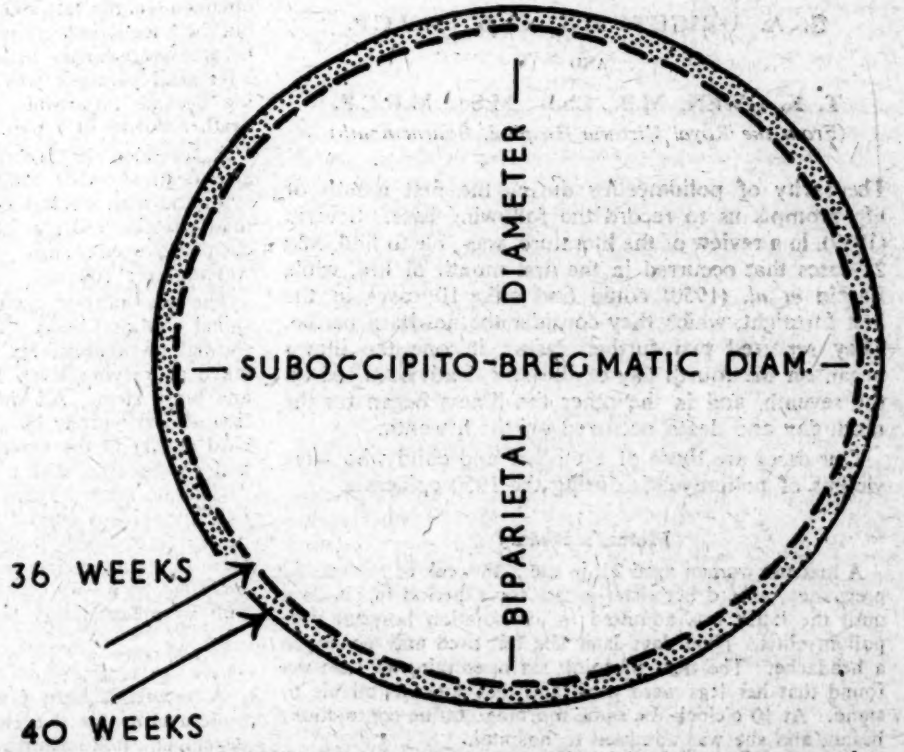

FIG. 4.—Actual size of the circumference of the average foetal head normally presented to the birth canal at 36 and at 40 weeks, showing increase as measured after delivery.

to the source of *x* rays, could produce a systematic difference between the measured and the true biparietal diameter.

This possibility has been put to the test by outlining the shadows thrown by three near-term foetal skulls in various positions relative to a source of light and then measuring the widest diameter at right angles to the longest diameter of the shadow. This measurement, with suitable corrections, is that used radiologically to determine the biparietal diameter. The measurements of the shadows showed that a difference of 4 mm. between the true and estimated biparietal could be produced—a significant difference in view of the fact that the mean growth of the biparietal diameter of the head from 36 to 40 weeks is also 4 mm. This observation could account for the failure to record by radiological means growth up to 4 mm. of the biparietal diameter during the period of descent of the foetal head.

Summary

The biparietal diameters of 1,059 newborn infants have been measured and plotted against the estimated duration of pregnancy.

Growth in this diameter of the foetal head occurs in the last few weeks of pregnancy.

An explanation is offered for the failure to detect by radiological means growth of the biparietal diameter of the foetal skull during the descent of the foetal head.

I wish to express my appreciation for the help given to me by the medical and nursing staff of Queen Charlotte's Hospital and of the maternity wards of Lambeth and Guy's Hospital.

REFERENCE

Josephs, S. (1949). *British Medical Journal*, 2, 1443.

POLIOMYELITIS IN MOTHER AND NEWBORN INFANT

BY

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AND

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The rarity of poliomyelitis during the first month of life prompts us to record the following case. Severin (1939), in a review of the literature, was able to find only 22 cases that occurred in the first month of life, while Baskin *et al.* (1950) could find only 10 cases in the first fortnight, which they consider the newborn period. They reported two further cases; in one the illness began on the fourth day of life and death occurred on the seventh, and in the other the illness began on the ninth day and death occurred on the fifteenth.

Our cases are those of a mother and child who were victims of poliomyelitis during the 1950 epidemic.

Mother's History

A married woman aged 21, in the 37th week of her second pregnancy, nursed her sister-in-law for a period of six days until the latter was admitted to an isolation hospital with poliomyelitis. Nine days later she felt tired and developed a headache. The next morning, on attempting to rise, she found that her legs were weak and that she was unable to stand. At 10 o'clock the same morning uterine contractions began, and she was admitted to hospital.

On admission her temperature was 99° F. (37.2° C.), pulse 100, and respirations 20. Labour proceeded normally, and the paresis involved the legs only. A male child weighing 7 lb. 4 oz. (3.3 kg.) was delivered normally at 7 p.m. after a quick second stage. At 8 p.m. she was noted to be dyspnoeic, with rapid shallow respirations, cyanosis, and pallor. Her temperature was subnormal, pulse 160, and blood pressure 140/80 mm. Hg. A small post-partum haemorrhage occurred before the completion of the third stage. She was given oxygen, but it became necessary to place her in a respirator at 1.30 a.m. the following day. By this time the muscles moving both hips, knees, and shoulder-joints, and the lower intercostal muscles, were all paralysed, but she was able to talk and swallow. The uterus was firmly contracted.

On the first day after delivery the temperature was 103° F. (39.4° C.) and pulse 100–130. She was given procaine penicillin prophylactically. The temperature fell to normal at the end of the third day after delivery, and remained normal. The pulse, however, was still between 120 and 140, finally rising just before her death on the sixth day after delivery.

At the post-mortem examination the lungs were moderately oedematous and congested. The stomach and intestines were very distended, chiefly by gas. The uterus showed normal involution. There were no other significant changes to the naked eye. Sections taken from the spinal cord and medulla showed the characteristic changes of poliomyelitis. A portion of the myocardium was taken for section, but foci of inflammation were not seen.

Infant's History

The infant was separated from the mother immediately after birth, and was kept isolated from her. He appeared well, with normal muscular power, and took his feeds until the eighth day, when he refused two feeds. His weight was then 7 lb. 12 oz. (3.5 kg.)

On the ninth day feeding remained poor, and the left arm movement was diminished. On the tenth day feeding became more difficult, though he was able to swallow food from a spoon at 10 a.m. The weight was 7 lb. 8 oz. (3.4 kg.). Later the same morning movements of the arms were completely absent, although a weak grasp reflex could still be obtained on the left side. No arm-jerks could be elicited, but the knee-jerks were present and equal. The baby rapidly became increasingly listless, and cyanosis developed. The intercostal paralysis was complete by 1 p.m. and swallowing became impossible. Oxygen therapy was given, but death occurred at 7 p.m.

A specimen of cerebrospinal fluid obtained immediately after death showed: 356 leucocytes per c.mm. (95% lymphocytes and mononuclear cells, 5% polymorphonuclear cells); total protein, 130 mg. per 100 ml.; albumin and globulin both increased; sugar, 50 mg. per 100 ml.; chlorides, 720 mg. per 100 ml.

The post-mortem examination revealed congestion of the spinal cord and brain. The heart and other internal organs showed no abnormality to the naked eye. Sections were taken at varying levels from the dorsal and cervical cord and brain stem. All showed foci of inflammatory infiltration almost entirely by polymorphonuclear cells, and in the cord chiefly in the anterior horns. Most motor-nerve cells had disappeared, but a few could still be identified in a degenerate state. There was some lymphocytic infiltration of the meninges around the cord. Similar lesions were also present in the medulla, pons, and thalamus. A section taken from the left ventricle showed some evidence of myocarditis, indicated by a very occasional focus of necrosis and infiltration by inflammatory cells, macrophages, and polymorphs.

Discussion

A record is here presented of a baby who developed poliomyelitis on the eighth day, born of a mother who developed poliomyelitis the day before delivery. The incubation period of poliomyelitis is generally believed to be about 10 days, but it may be as short as five. Although

the baby was removed from the mother as soon as possible it seems probable that the infection was acquired by contact at birth rather than due to intrauterine transmission. Of particular interest is the myocarditis in the infant. Saphir and Wile (1942) first drew attention to the occurrence of myocarditis in poliomyelitis, but it is by no means constant. Saphir (1945) described myocarditis in 10 of 17 patients examined after death. The second case reported by Baskin *et al.* showed histological evidence of severe acute and healing myocarditis. The lesions in the heart in the case here reported were widely separated and could not be described as severe, the intervening muscle being normal. The child died from bulbar paralysis and not myocardial failure.

REFERENCES

Baskin, J. L., Soule, E. H., and Mills, S. D. (1950). *Amer. J. Dis. Child.*, **80**, 10.
Saphir, O. (1945). *Amer. J. Path.*, **21**, 99.
—— and Wile, S. A. (1942). *Amer. J. med. Sci.*, **203**, 781.
Severin, G. (1939). *Nord. Med. (Hygiea)*, **1**, 55.

Medical Memorandum

Spontaneous Rupture of the Spleen

A case of spontaneous rupture of an apparently normal spleen is recorded because of the comparative rarity of such a condition. Cases have been reported from time to time, and about 40 cases have been recorded within the past 20 years.

CASE REPORT

An agricultural labourer aged 46 was admitted to hospital on January 8, 1951, at about 1 a.m. He had felt off colour for about a week, and had had a headache followed by repeated bleeding from both sides of the nose. Two days before admission he felt pain in the epigastrium after moving some milk-churns, but this passed off, leaving him feeling as though he had influenza. He had some pain in the back all next day and stayed in bed, still thinking he had influenza. The same night at 10.30, while in bed, he felt a sudden severe pain beneath the left costal margin and in the praecordium. He got out of bed and fainted. He was admitted as a case of possible perforated gastric ulcer. In his own words, he had always been "as fit as a fiddle." However, on closer questioning he admitted having been ill with malaria for 10 days in 1926 while serving in the Army in India; there had been no recurrence.

On examination he looked pale and ill; he had marked dyspnoea, and felt faint when sat up in bed, but did not seem notably anaemic, being rather dark-skinned. His temperature was 98° F. (36.7° C.), pulse 100, and respirations 25. The heart sounds were faint, the rhythm was regular, and the pulse beat was soft. There were a few crepitations at the left base, with slightly diminished breath sounds and impairment of the percussion note. The abdomen was very rigid all over the epigastrium and deep palpation was not possible. The liver dullness was not altered, and bowel sounds were present. There was no shifting dullness. He had been able to drink tea without nausea or any worsening of his pain.

Perforated gastric ulcer was not thought to be the diagnosis, but possibilities considered were early diaphragmatic pleurisy, coronary thrombosis, or, possibly, acute pancreatitis. Operation was not carried out at once because it was thought he would not survive a laparotomy without resuscitation. *X*-ray films of the chest and abdomen taken later in the morning showed no abnormality, and a leucocyte count showed total cells, 11,000 per c.mm. (polymorphonuclears 75%, eosinophils 2%, basophils 1%, monocytes 5%, lymphocytes 17%). Perforation was therefore thought to be most unlikely, and the patient was kept under observation. His condition did not deteriorate, and he took tea by mouth without discomfort or vomiting. The next day his condition was slightly better, but he still had the abdominal pain and rigidity. The bowel sounds were also present. At a consultation with the medical specialist, Dr. A. H. Banton, coronary thrombosis and pleurisy were excluded. As the patient was now more fit a laparotomy was arranged. After preliminary intravenous saline he was taken to the theatre with the drip *in situ*—the tentative diagnosis being acute pancreatitis.

Operation.—On February 9, under thiopentone, nitrous oxide, and curare anaesthesia, a midline upper abdominal incision was made. The peritoneal cavity was found to contain free blood. This was traced to a spleen surrounded by enormous clots. Accordingly blood was transfused instead of saline, and the approach to the spleen was rapidly improved by a transverse incision through the left rectus muscle. The bleeding had taken place between the spleen and its capsule, and the huge clots were mostly intracapsular. After separating these a normal-sized spleen came to view; the pedicle was ligated and the spleen removed after separating the adhesions which were anchoring the capsule to the diaphragm. The spleen looked normal and appeared to have bled from its surface, there being no appreciable rupture in its substance. The adhesions of the splenic capsule to the diaphragm were remarkable for small pearly nodules of fibrous tissue of an icing-sugar appearance. After removing much blood from the peritoneal cavity the abdomen was closed. Altogether 5 pints (3.3 litres) of blood was transfused into the patient, who made a quick and uneventful recovery.

Pathological Report (Dr. E. J. Harries).—"Spleen of about normal size. Capsule shows slight perisplenitis. On section, dark red. Some blood clot remains attached to outside of capsule. Also fragments of tissue from diaphragm. Microscopical examination: The splenic capsule is thickened, but is lost over most of the organ. The haemorrhage seems to have been mainly subscapular but has split the capsule, leaving a thin 'pseudo-capsule' limiting the parenchyma. Stains reveal free iron in and on each side of the capsule, suggesting that the haemorrhagic accidents have at least a slightly longer history than the clinical history suggests. The parenchyma shows reticulum hyperplasia but no definite evidence of specific disease such as malaria. The arterial system in the organ appears normal. The diaphragmatic fragments are similar to the thickened capsule described, and are probably adhesions which have in the past separated and become smoothed off."

COMMENT

There was evidence of previous disease only so far as the perisplenic adhesions are concerned. Furthermore, it is reasonable to assume that the capsule may have been torn from the spleen while the patient was lifting the milk churns, though this was a normal part of his work. The bleeding was slow until the capsule ruptured 36 hours later; the severe pain then came on, associated with signs of shock. These findings fit in with those of Babson and Morgan (1946). It is possible also that the perisplenic adhesions may have originated during a short attack of malaria, 25 years previously, though this was not a pathological malarial spleen in any other sense. A perusal of the literature of the past eight years suggests that there may be two pathological types of spleen which rupture spontaneously: those with intrasplenic haemorrhages in a physiologically engorged spleen or a spleen with diseased vessels, the haematoma separating the capsule late; and those which produce extrasplenic haemorrhages from the surface of the spleen, separating the capsule early. Both types occur either with dramatic suddenness or with preliminary malaise, depending on how long the bleeding goes on before the capsule ruptures.

In the above case it is likely that the splenic capsule was torn from an engorged spleen by the trivial effort of moving a milk churn.

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REFERENCE

Babson, W. W., and Morgan, P. (1946). *Amer. J. Surg.*, **72**, 97.

Reviews

LEONARDO DA VINCI

Leonardo da Vinci on Movement of the Heart and Blood. By K. D. Keele, M.D., F.R.C.P. Foreword by Charles Singer, M.D., F.R.C.P. (Pp. 142; 68 illustrations. £4 4s.) London: Harvey and Blythe. 1952.

Leonardo da Vinci, one of the most gifted beings ever born into the ranks of mankind, was the illegitimate son which a country girl bore to a Florentine notary on April 15, 1452. In his youth he studied the anatomy of the human body in order that he might give a just expression to its movements in all moods and tenses. In this his idealism succeeded in giving a grace and beauty to the human figure beyond that ever attained by Nature. He was blessed (or cursed) by a restless, insatiable curiosity and in his maturer years developed into a military and civil engineer, wherein he found vent for a fecund inventive faculty. It was during this maturer period that Leonardo returned to the study of the human body, this time not as an artist but with knife and forceps in hand as an anatomist, resolved to understand and explain the workings of the human body. As he dissected he drew, giving clear expression to the structures his knife laid bare, making drawings that are quite modern in their technique, drawings such as were never made before his time. As he dissected he added rough notes to his drawings for his private use when he came to systematize his inquiries. These notes were made from time to time as opportunity for dissection occurred; altogether he claimed to have dissected 30 subjects. These anatomical drawings and notes are the subjects discussed by Dr. Keele in his text and represented in the 68 plates which adorn his monograph.

Leonardo died in France in 1519, at the age of 67; at his death his manuscripts passed into private ownership, where they remained for fifty years. In the meantime Vesalius appeared (1514–1564) and laid the basis of modern human anatomy. Had Leonardo made his discoveries known in his lifetime it would have been he and not Vesalius who would have been regarded as the Father of Human Anatomy.

Dr. Keele has made Leonardo's work on the heart and vessels the chief subject of his text. He reproduces 82 drawings or sketches which Leonardo made of the valves of the heart. All the valves are declared to be cunningly constructed and, in the modern sense, competent. Yet Leonardo held the opinion that the ventricles emptied their load of blood into the auricles, which the auricles duly returned, great friction being thus caused, turning the heart into a machine for heating the blood and thus maintaining the temperature of the body. He recognized that the ejection of blood by the left ventricle was the cause of the pulse felt at the wrist and yet remained adamant in the Galenical conception that in both arteries and veins the blood, like the tides, ebbed and flowed. Leonardo was a realist and also an idealist; his mind felt no difficulty in reconciling contradictory facts with favoured convictions. His two drawings of the veins and arteries of the human body are as Galen imagined them, not as Leonardo must have noted with his own eyes.

ARTHUR KEITH.

BRAIN METABOLISM

Brain Metabolism and Cerebral Disorders. By Harold E. Himwich, M.D. (Pp. 452; 52 figures. £2 6s. 6d.) London: Baillière, Tindall and Cox. 1951.

This book will be welcomed as the first of its kind in a field that is now receiving increasing attention. It describes a good deal of experimental work that has not appeared in any textbook before. The book is divided into two parts: in Part I the author gives a detailed review of the biochemical mechanisms by which glucose is utilized to supply the energy required for the activity of the brain. He amply supplements this by reference to clinical data, by a section on the electrical activity of the brain, and by chapters on the brain circulation and the brain metabolism in man. In Part II he chooses for special attention the sequence of clinical signs and symptoms seen in insulin hypoglycaemia, anoxia, and anaesthesia. Here a wealth of experimental data on the effects of the barbiturates, alcohol, and other drugs are interpreted in the light of Hughlings Jackson's hypothesis of the phyletic organization of the central nervous system and "dissolution from the highest level."

The scope of the book is less than might be inferred from the title, for it contains relatively little about psychiatric conditions and omits discussion of a good deal of recent work on brain metabolism, such as that from the Scandinavian and other European laboratories. Of the 1,042 references, more than 100 refer to publications from Dr. Himwich's own laboratory. But the subjects chosen for inclusion are discussed with painstaking care and with the authority of an author qualified by over 25 years' experience in this field.

DEREK RICHTER.

SISTER KENNY

And They Shall Walk. The Autobiography of Sister Elizabeth Kenny, written in collaboration with Martha Ostenso. (Pp. 268. 15s.) London: Robert Hale. 1951.

The autobiography of Elizabeth Kenny is the story of how a woman living in an unfrequented part of Australia became known throughout the world for her skill in the treatment of poliomyelitis. It is intended chiefly for the layman and no attempt has been made to explain the technicalities of her work. Miss Kenny came from a family that had settled in New South Wales and later moved to Queensland. At a fairly early age she became deeply conscious that her mission in life was the relief of suffering and of paralytic disorders in particular. After a period of strenuous service in the first world war, her account of which is perhaps the most generally interesting part of her narrative, she settled down to the work with which her name will always be connected. Even more than the rest of us, she learned as she went along. With altogether remarkable insight she recognized a clinical feature of poliomyelitis, which she called muscle spasm, that had previously eluded most experienced observers; and, much more important, she drew attention to the harmfulness of immobilization in the treatment of paralysed muscles.

On the basis of these two observations she rather rashly elaborated a theory of the pathology and treatment of the disease. Miss Kenny epitomized the cardinal features of poliomyelitis as muscle spasm, incoordination, and mental alienation. The paralysis consequent on damage to the spinal cord seems somehow to have been regarded as a minor affair. She tells us that at no time did she claim to cure the disease, but the widespread publicity that always attended her was often less accurate.

There is, however, no doubt that Miss Kenny's influence on the treatment of poliomyelitis (and of other lower-motor-neurone disorders) has been thoroughly healthy. She successfully challenged the wholly illogical idea that a paralysed part must be immobilized; she showed that contractures may be caused by paretic or paralysed muscles, and if what is sound in her practice was universally practised to-day we should be well on the way to abolishing one of the most serious consequences of paralytic disorders—namely, deformity. The abandonment of rigid fixation of the paralysed part, so long a sacred tenet of the Liverpool school of orthopaedics, is a great step forward, and for this we are indebted to this shrewd and forceful lady. Her other discovery, concerned with the irritable state of affected muscles, which she called spasm, is less significant. Miss Kenny herself regarded it as a constant feature of the disease, but, while the accuracy of her observations has been amply confirmed, it is certain that muscle spasm is often absent and that when present its duration is often

short and unconnected with the progress of recovery. If severe or persistent, it is, as she insists, a potent precursor of contracture and hence of deformity.

An autobiography requires that a reviewer shall pass judgment on the character of the writer. Sufficient has already been said to give some notion of the worth of Miss Kenny's work, and the durability of all (and that is the greater part) that is good in it. Yet although she has achieved a wider reputation than other great humane women of our time, such as Dame Agnes Hunt and Lady Allen of Hurtwood, its quality is inferior. These two great Englishwomen have been every bit as tenacious, every bit as impatient of red tape and professional complacency, but they finally got their way by cheerful persistence and by inspiring that greatest of all reforming forces—affection. Miss Kenny's story, as recorded, ends on a triumphant note; but it is necessary and lamentable to add that at a later date she became fatally estranged from the National Foundation for Infantile Paralysis, the organization which, as she herself tells us, had treated her with princely generosity—and she outlived her welcome in the United States. Miss Kenny lacked two of the qualities of greatness. She was never content to let the idea sink in and do its work; she hammered everybody with the whole powerful apparatus of modern propaganda—the Press, the radio, the cinema—until finally even the Americans, good-humoured and tolerant, and with a very high threshold to that sort of thing, got sick of it. The other trouble was that, if her story is strictly accurate, she never made a mistake.

It is a pity that this account of a strenuous life of many long journeys and of arduous pioneering is not written more graciously, and some readers will be irritated by the frequent misspelling of the names of well-known people. Yet no one will fail to be moved by the single-mindedness of this woman who, undeterred by many initial disadvantages, devoted her life to succouring the victims of one of the most heart-breaking scourges of our time.

H. J. SEDDON.

EFFECTS OF SMOKING

Tobacco and the Cardiovascular System. The Effects of Smoking and of Nicotine on Normal Persons. By Grace M. Roth, Ph.D. (Pp. 66. 16s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1951.

It is a curious thing that most people regard with distaste any scientific analysis which smacks of criticism of things they like. Evidence that those who drive cars at high speeds are dangerous is often resented quite fiercely. Evidence that an odd drink or two blurs the car driver's judgment and slows his reflexes is unwelcome. Likewise the collection of evidence that cigarette-smoking has any physiological effect at all is regarded as not playing the game.

Smoking is very popular. We do not keep records in this country, but in the U.S.A. the Department of Agriculture states that 358 billion cigarettes were smoked in 1949, or 3,400 for each man and woman in the country. Hence nicotine is a very widely used drug.

Miss Roth's small book gives an account of her observation that smoking cigarettes raises the pulse rate, raises the blood pressure, and leads to vasoconstriction in the skin and to a fall of skin temperature. There is nothing surprising in this, since it has been well known since Langley's work in the nineteenth century that nicotine stimulates sympathetic ganglia, from which these effects might be expected. But, while the blood pressure and pulse rate at once return when smoking stops, the constriction in the skin often persists for a long time, and we are left with a suspicion that this constriction may be due to something else than ganglionic stimulation. Miss Roth, however, makes no reference to the evidence that nicotine releases vasopressin from the posterior lobe of the pituitary, although this might well explain the prolonged effect.

Some surprising statements are made about the amount of nicotine taken into the mouth in smoking one cigarette. It is put as high as 4.4 mg., of which "2.5 to 3 mg. is absorbed by the lungs." No evidence is given in support of these figures, which are much greater than those obtained by Ling and Wynn Parry, whose work indicates that the amount of nicotine entering the mouth is not more than 1 mg.

It is unfortunate that the author of this attractively bound little book does not discuss the subject more thoroughly.

J. H. BURN.

HEREDITARY EYE DISEASE IN TASMANIA

The Significance of Heredity in Ophthalmology. A Tasmanian Survey. By J. Bruce Hamilton, M.D., Ch.M., D.O., D.O.M.S., F.R.A.C.S. (Pp. 135. £2 10s.) Melbourne, Australia: A. H. Massina and Co. 1951.

Dr. Bruce Hamilton has devoted many years and much thought to the study of hereditary blindness in Tasmania. He has had the advantage of dealing with a relatively small population, but the considerable disadvantage that it was scattered over a large territory. In this monograph he gives full details of the background of his work, the personal histories of the members of the families he has investigated, and extensive pedigrees. Excluding the refractive errors, and squint in its various forms, he has been able to find examples of some 16 genetic eye diseases in his material, and the 118 pedigrees presented contain some that are of exceptional interest, such as the sibship of retinal detachment with cystic changes in the lungs, and the occurrence of sarcoma of the choroid in a woman and her niece. His pedigrees on chronic dacryocystitis are likewise of interest, since relatively few of these are available. In other conditions the information follows the classical patterns; among these the pedigrees on Leber's disease are particularly valuable.

ARNOLD SORSBY.

NATIONAL HEALTH SERVICE

The Health Services. A compendium of conference papers with additional chapters published for the Institute of Public Administration. Introduction by Henry Lesser, C.B.E. (Pp. 136. 10s. 6d.) London: George Allen and Unwin. 1951.

This small book is one of the many useful publications issued by the Institute of Public Administration. It consists mainly of papers read at a conference organized by the Institute and held in March, 1951, to discuss some of the practical problems of the health services. Mr. Henry Lesser presided, and has written a wise and thoughtful foreword.

There are 12 papers, each written by a contributor whose work and experience qualifies him or her to do so expertly and authoritatively. The many difficulties which have arisen in connexion with the health services are discussed with a high sense of responsibility, and in general criticism is constructive and the many problems are considered sympathetically. As Mr. Lesser points out, there are bound to be difficulties and mistakes, but there has been great achievement too.

Perhaps the greatest danger threatening the ultimate success of the new Health Service is the impact of the current economic crisis. The chapter on financial problems is therefore timely and important. The author, Mr. François Lafitte, chairman of the P.E.P. Health Group, discusses what he calls the "spending spree" stage of the Health Service. All his views will not commend themselves to everyone, but his careful survey of the financial situation and his able and at times vehement advocacy of reform provide a lucid and valuable contribution.

This symposium is worthy of careful study by both clinicians and administrators in all branches of the Service. It deals in the main with problems which are but transitory. Its value, which is high now, will therefore diminish progressively as the problems are solved.

C. METCALFE BROWN.

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LEONARDO DA VINCI

April 15 is the fifth centenary of the birth of one of the most remarkable beings that has ever lived. For such was indeed Leonardo da Vinci, who first saw the light in 1452. He was the illegitimate son of a peasant girl, and from his childhood showed extraordinary intelligence, beauty, and vigour. His father, member of a well-to-do Florentine legal family, later married a woman of his own class, but Leonardo was early accepted as one of his father's household. Nevertheless his education was certainly defective, since he had acquired no Latin—a very serious handicap in that time when it was the only medium of learning. This lack may well have been a consequence of his own waywardness, but it does correspond to the one weapon missing from his intellectual armoury. For, even if we allow for any educational gap, it is a fact that in his notebooks, five thousand pages of which survive, his literary standard is surprisingly low, especially in contrast with his superb command of the pencil. It is evident that his very active mental life was overwhelmingly visual. His immense and varied intellectual powers could express themselves freely only by graphic methods.

For some years and from about the age of 14 he worked in the studio of that versatile artist Verrocchio, who himself dissected the superficial muscles of the human body. In 1472 Leonardo was brought into contact with a varied society by being admitted to the Company or Guild of Painters of Florence. The guilds in that city had an extremely elaborate organization, and the painters were united, in a complex way, with the dealers in spices, with the physicians, and with the apothecaries. All these were connected with the service of the hospital of Santa Maria Nuova, where Leonardo's first dissections were performed. Among his numerous and immense activities medical men will naturally be most interested in his physiological and anatomical researches. The surviving records of these are nearly all contained in manuscripts in the Royal Library at Windsor Castle. They have been reproduced in eight superb folio volumes of facsimile, many of the best pages of which are now displayed in the East Gallery of the Royal Academy. These exhibits include, however, an original drawing, specially lent by Her Majesty the Queen, representing a child in its mother's womb. It is a picture of most moving beauty in which the child seems to be dreaming the thoughts of the race that is to come. Despite certain errors of detail, notably in the whimsical division of the placenta into cotyledons, it is perhaps the most beautiful anatomical figure of all time.

Leonardo's anatomical researches may have begun about 1472. By 1489 he was planning a work on the subject which many of these drawings were doubtless intended to illustrate. Alas, it never appeared, though he continued his anatomical researches at least until 1513. Nor was his interest only in the structure of the body. Being a child of his age, he could not fail to be influenced by the universally accepted and highly ingenious physiological system of Galen, but he made many experiments to test its accuracy. Notably some of his results raised the problem of the mechanism of the heart-beat and, in certain important respects, anticipated Harvey. It is not too much to say that had Leonardo's anatomical work been published the discovery of the circulation would probably have been made in the sixteenth century instead of being deferred till the seventeenth, for there were several experimenters at work on the subject between Leonardo and Harvey, not least of them being Vesalius, who came almost exactly at the mid-point in time between them.

In estimating the anatomical and physiological achievements of Leonardo we must not forget that they formed only a fraction of his scientific activities, which in turn formed no more than a fraction of his total activities. The contents of his notebooks bear witness to the part that science and engineering played in his life. He aimed to publish books on mechanics, on the flight of birds, on the elements of machinery, on perspective, and so on. But with them, as with anatomy, the urge to ever fresh investigation interfered with their expression. The interpretation of his manuscripts was moreover long delayed because of his use of mirror writing, apparently adopted as a sort of cipher but relatively easy for him to write, since he was left-handed.

Leonardo dissected more than thirty human bodies. He was busy on this task both at Florence and Milan. Though he was far from being the first of his age to study the structure of the human body, he was certainly the first in modern times to do so on scientific lines. Before him dissections, both "academic" and "artistic," had long been practised. Academic dissections were literally demonstrations. The academic official, literally a "reader," declaimed the authorized text while his demonstrator pointed out, as his title implies, the organ described. All this was done in

public and had to be hurriedly completed in daily sessions on four consecutive days. The students had no direct contact with the part. Leonardo had read the current text for this ceremony, an Italian translation of which was available. On the other hand several earlier artists and some of his own time, including his own master, Verrocchio, anxious to represent the human body correctly, did indeed examine the bones and the surface muscles of flayed corpses. Many of the great works of art of the Renaissance betray the anatomical knowledge thus acquired. But Leonardo went far beyond either the academic or the artist anatomists. He studied the body throughout and in detail. He sought to understand its intrinsic structure by observation and experiment, both prolonged and systematic. His marvellous facility first in visualizing and then in drawing enabled him to superimpose the various structures and tissues on each other in the three dimensions of space. Thus for the first time in history he was able to prepare figures, drawn in true scientific perspective, showing the relations of the parts to each other. In this sense he was the very first anatomist, for even the greatest of the ancients had no such visual aid.

Unfortunately Leonardo never finished anything, and least of all his great anatomical researches. He had not that power of limiting objective which is essential to the strategy of science. His mind so teemed with ideas and with newly observed facts, gathered by his vast industry, that the very channels of expression were blocked. His great discoveries remained *almost* unknown till the nineteenth century.

Almost but not quite. One whose personality aroused so much curiosity, who gave so much time to recondite and unusual studies, could not dissect over thirty bodies without some information about his activities becoming widely known. Neither Florence, nor Milan, where many of his researches were made, were then seats of universities, though they were certainly well-developed seats of gossip. In any event Leonardo would have been the last to make impact on the rigid structure of an academic society. But Leonardo's methods were naturally still known and still spoken of in the studios when 13 years after his death the anatomist Vesalius came to Italy. There he met a fellow-countryman, an artist, who was imbued with the tradition of Italian painting which still looked back to Leonardo. The two men between them seemed to reconstitute one aspect of the spirit of their mighty predecessor. Thus scientific academic anatomy was born with a backward glance at its real father.

The Exhibition at the Royal Academy to celebrate the quincentenary of Leonardo's birth was proposed by the Science Museum. This union of Art and Science is peculiarly appropriate to the man that it commemorates. Most of the original works are from the Royal collection, though two of the finest are the property of the Academy itself. The anatomical section has been arranged by Dr. K. D. Keele, whose book on Leonardo is reviewed in this issue by Sir Arthur Keith. In connexion with the exhibition a series of lantern lectures is being given in the Senate House of the University of London. Of these, a specific medical interest is attached to those by Dr. K. D. Keele on "Leonardo's Researches on the Heart and the Blood" on April 24, and that of Professor Charles Singer, who closes the series with his "Leonardo and the Structure and Action of the Human Body" on May 29.

Leonardo puts himself in his historical position in words which, with but slight paraphrase, may be read as prophecy.

"You who would despise my drawings as teaching anatomy and say that it is better to look at dissections than drawings, would be right were it possible to see all the details in your dissections. But you will not see more than a few structures, whereas I have dissected many entire human bodies, down to the very smallest particles of flesh. For it was necessary to proceed by stages with as many bodies as would make my knowledge complete. Can you do likewise? For if you be interested in the subject you may be deterred by repugnance. If this do not restrain you, maybe you fear to pass many night hours, as I have done, in the company of corpses, flayed and hideous to look upon. If this deter you not, perhaps you lack the skill in drawing, essential for such work. And even if you have this skill, you may lack knowledge of the laws of perspective, or of the mechanical laws to estimate the action of muscles in movement. Or again and above all, you may lack patience. As to whether these things have been found in me, the books that I have written will give their answer, Yea or Nay. For in all these I have been hindered neither by avarice, nor by sloth, nor by fear, but only and always by time. Farewell."

The answer will be given to any who will visit the wonderful exhibition at Burlington House and attend the course of lectures on the man and his works at the University of London.

FATIGUE

The Ergonomics Research Society has as its objects the promotion and application of knowledge about man and his working environment, including the design and use of equipment with which a man works and the conditions in which he works. The Society recently organized a symposium[1] on "Fatigue"

[1] The *Proceedings* of the Symposium will be published eventually by the Ergonomics Research Society.

which was attended by members from many countries, and a report of some of the discussions appears on another page.

While most would be willing to accept that fatigue or tiredness follows continued work, whether muscular or mental, it is difficult, as Sir Frederic Bartlett pointed out in an opening address, to find a completely satisfactory definition of fatigue. Fatigue can be used as a term to cover determinable changes which can be attributed to continued activity. The activity may deteriorate or it may alter its character and show unwanted side-effects. The type of extreme muscular fatigue with which the physiologist is familiar occurs less often in industry than formerly because of increased mechanization. Nevertheless, there are still some heavy tasks in industry, made heavier when they have to be performed in adverse environments. In these cases something can be done to avoid or lessen fatigue by prior assessment of the physiological load imposed by the tasks and by the selection of workers who are fit to undertake these tasks and to withstand the environmental stress. But work which is rapidly exhausting can be undertaken only if suitable rest periods are arranged. Time and motion study may help to show the most economical way of performing it.

Some contributors to the symposium spoke about the additional stress imposed by the environment. High temperature and humidity affect fatigue, as measured by industrial output, and the incidence of absenteeism, accidents, and sickness is increased when the temperature is unpleasantly high. The efficiency and the sense of well-being of men in the Services deteriorate during prolonged sojourn in the Tropics, and, although some of the effects are psychological, hard muscular work may add to an already severe physiological stress caused by the environment. Although tropical deterioration may be due in part to prolonged exposure to trying heat, the effects of a short exposure to something resembling a tropical climate can be produced in the home for a few hours during the family washing day.

In attempting to assess fatigue by measurement of performance, or by the imposition of specific tests, it is important to appreciate what has been generally overlooked—that there may be alterations in the pattern of doing the work, or that other signs of fatigue not directly concerned with the work may appear, before there is obvious deterioration in performance. Thus in simple experiments with the ergograph alterations in performance, such as a slowing of the change from contraction to relaxation, may appear before there is any reduction in the strength of contraction. And the onset and development of fatigue depend not only on the severity of the work but, to a great extent, on the worker's attitude to his job.

Many papers dealt with the assessment of what might be termed psychological fatigue. Often quite light muscular work, or mental work requiring close attention, can be carried on continuously only at the cost of reduced output, more frequent mistakes, boredom, monotony, or irritability. This problem caused great concern during the war when men and women were required to spend long operational periods—for example, as radar observers, as Asdic and wireless operators, or as pilots flying by instruments—when observations had to be made at irregular and widely scattered intervals and acted upon with few mistakes. Researches designed to test the influence of factors such as the duration of the working period, the number and display of instruments, and the environment on alertness and on the accuracy and speed of responses to signals led to some notable conclusions. For many sensory tasks and for others necessitating observation and movement there was a significant fall in efficiency after twenty or thirty minutes. The individual, however, was not aware of his mistakes; on the contrary, he might be optimistic about his performance. On the other hand, experiments showed that attention to the whole field to be perceived became more difficult. Changes in the situation were not quickly appreciated and the timing of consequent reactions became disturbed, particularly if the observer or operator had to keep pace with a set sequence of changes in the field displayed to him.

Later the subject often complained of aches and pains and general discomfort, and it is possible that proprioceptive impulses which at one stage were used unconsciously in the performance of the task, or were merely present incidentally, were now exaggerated and obtruded into consciousness. In the early stages of the test the individual was working as a well co-ordinated whole. As fatigue ensued it appeared that stress began to show in the central nervous mechanisms: from what is known about vision it appears that the failure is not in the peripheral mechanisms. The stress may show itself in part as a tensing of some muscles not necessarily directly concerned in the task, and attempts have been made to examine the condition by electromyography. Sometimes, if the subject is aware of the deterioration in performance, he may make greater efforts, which, while giving a temporary improvement in performance, increase the stress. Poor illumination, high external temperature, and uncomfortable posture or support also increase it.

The concept of stress should not be confined to psychological considerations. In the continued performance of hard muscular work many adjustments are made in the circulatory, respiratory, and thermoregulatory systems in order to maintain an oxygen supply to the muscles adequate for their rate of working and to prevent an undue rise in body temperature. But the relevant increases in the output of the heart, in lung ventilation, and in cutaneous vasodilatation and sweating take up some of the reserve which the body normally has in hand. For example, once the transport of oxygen fails to keep pace with the liberation of energy in the muscles, or the rate of heat loss through the skin falls behind the rate of heat production in the body, deterioration in performance must begin even though temporary improvement may be brought about by various expedients.

The study of fatigue is helped by regarding the body as being in a state of dynamic equilibrium which is the resultant of many factors. Disturb any of these and the balance is upset; equilibrium is regained or maintained only by a redistribution and resetting of the factors. Superficially there may be little sign of change, but the development and the application of specific tests may show that, in order to maintain the new condition of equilibrium, stress has been put on certain mechanisms. A limit to the maintenance of equilibrium may be set by any one factor being forced to the extremity of its range of operation. In addition, the operation of, and the intensity of the effects produced by, these factors will be determined not only by the present condition of the individual but also by his past history and by what he anticipates for the future. Fatigue is a state which affects the whole man and not merely his parts studied in isolation.

MECHANISM OF ANAPHYLAXIS

Before and during the first world war a great deal of work was done on the part the products of proteolytic digestion found in the blood plasma played in the production of anaphylactic shock. One of the hypotheses widely held was that both antigen-antibody reactions and such substances as agar, starch, or kaolin (which when rubbed up with serum produce "anaphylotoxic" sera) brought about an activation of the plasma enzyme protease, which then produced toxic substances in the blood.

Following Dale's classical work upon the similarity of the effects of anaphylaxis and of histamine, and the demonstration that histamine is actually released when antigen is added to perfused sensitized guinea-pig tissue *in vitro*,[1] the problems of anaphylaxis appeared in such a clear, fresh light that most workers ceased to probe into the murky shadows occupied by proteases and the formed elements of the blood. The mechanism of "anaphylactoid" phenomena appeared meanwhile to have been solved by the observation that many of the agents which produced these phenomena caused minute thrombo-emboli consisting largely of platelets and leucocytes. Supposedly these mechanically obstructed the flow of blood through the pulmonary and other capillaries. Anaphylaxis and anaphylactoid phenomena thus appeared to be separate and distinct.

Interest in the part played by humoral as opposed to cellular factors was revived by workers who had continued to study anaphylactic and peptone shock in the dog. Among these was Dr. Rocha e Silva, whose article elsewhere in this issue contains a historical review of some of the work which has brought platelets, leucocytes, and "anaphylotoxins" back into the limelight. He and his collaborators showed that histamine and heparin are released in large amounts by perfusion of the isolated liver of a sensitized dog with antigen solution, provided the perfusion fluid contains all the formed elements of the blood. This release of histamine is accompanied by the formation and rapid disintegration of micro-thrombi of leucocytes and platelets in the liver capillaries, and at the same time the plasminogen of the plasma becomes activated. The scale of the histamine release appears far to exceed the amount available from the disintegrated leucocytes and platelets alone, and Rocha e Silva supposes that a general histamine-releasing agent is produced from the platelet disintegration.

A rather similar clumping of platelets and leucocytes has been shown to occur in rabbits at skin sites prepared for the Shwartzman phenomenon by injection of meningococcus filtrate, or at the site of reinjection of antigen into a sensitized animal; in both cases intravenous injection of the appropriate agent results in a considerable temporary diminution in the numbers of circulating leucocytes and platelets.[2] Furthermore, previous removal of platelets by means of anti-platelet serum, or of polymorphonuclear leucocytes by nitrogen mustard, has been shown to prevent the development of the Shwartzman phenomenon and, according to Stetson, of the Arthus phenomenon also.

Pursuing the idea that platelet disintegration and plasminogen activation somehow produced a plasma with anaphylotoxic properties, and presumably equating in this "anaphylotoxins" prepared by different means, Rocha e Silva and his colleagues proceeded to test, by perfusion through isolated guinea-pig lungs, sera which had been incubated with agar. They found that such sera released very large amounts of histamine under these conditions, and would apparently even release histamine from the isolated guinea-pig ileum. During the course of this work it was noticed that the presence of citrate appeared to protect platelets from disintegration and also to prevent the development of anaphylotoxic properties in sera. On this basis, Rocha e Silva suggests that citrate might be used therapeutically.

[1] Bartosch, R., Feldberg, W., and Nagel, E., *Pflüg. Arch. ges. Physiol* 1932, **230**, 129.
[2] Stetson, C. A., *J. exp. Med.*, 1951, **94**, 347.
[3] *J. Physiol.*, 1949, **109**, 190.
[4] Ibid., 1939, **95**, 393.
[5] *C.R. Soc. Biol., Paris*, 1950, **144**, 1295.

The discovery by MacIntosh and Paton[3] in 1949 that a number of fairly simple organic bases, and in certain circumstances heparin, are able to liberate histamine has strengthened the concept of the importance of histamine-liberators. There remain, however, many points to be cleared up before the hypothesis put forward is likely to find general acceptance. The release of histamine from many organs of the sensitized guinea-pig upon addition of antigen *in vitro* was demonstrated by Schild,[4] and recently Feldberg and his co-workers at the National Institute for Medical Research have demonstrated the release of large amounts of histamine from the isolated skin of sensitized dogs when antigen is perfused through it. In neither of these cases does it seem possible that leucocytes or platelets could be involved, and only traces of plasma could have remained in the organs after washing.

These experiments do not exclude the formation of histamine-liberators as intermediates, but the mechanism can hardly be exactly that proposed by Rocha e Silva. It may well be that more than one mechanism is involved, and that the importance of the mechanisms varies with different species of animal. Other questions which might be asked are whether platelets and leucocytes are both involved; whether the hypothesis is extended to cover chronic as well as acute allergic reactions; whether there is truth in the statement by Adant[5] that sera do not develop anaphylotoxic properties if bacteria are excluded during incubation; what the histamine-liberators are and how they are formed; and whether histamine release is the whole story. Nevertheless, there is a striking similarity between the lists of substances (including, for example, chloroform, antigen–antibody mixtures, agar, and inulin) which produce anaphylotoxin, which evoke the Shwartzman phenomenon, which activate plasminogen, and which cause clumping of leucocytes and platelets *in vivo* and segregation in the capillaries of the lungs and other organs. One of the attractions of the hypothesis discussed by Rocha e Silva is that it attempts to bring all these phenomena into a single explanation.

THE SCHOOL OF HYGIENE IN ATHENS

It is gratifying that a definite move has been made towards the reorganization of the School of Hygiene in Athens. The economic state of Greece due to the effects of wars over a long period is still such as to retard the repair of extensive damage to many buildings, roads, and services, but the return of the school to its former very high standard for which it was renowned is a matter of great importance to the country. The school was founded in 1929 with the encouragement of the Section of International Health of the League of Nations and the Rockefeller Foundation. During the years of war and occupation the buildings were badly damaged and the staff scattered. Later, as a result of collaboration between the Greek Government, the World Health Organization, the Rockefeller Foundation, and the Public Health Division of the Economic Co-operation Administration (now the Mutual Security Agency), a plan was drawn up by which Marshall Aid funds were allotted to the repair of the school buildings, and in addition $12,000 worth of equipment was provided. Brigadier G. S. Parkinson, who was a member of the staff of the London School of Hygiene and Tropical Medicine from the date of its inception and was thus well fitted to survey the conditions prevailing in the Athens School and to understand its difficulties, was then invited to visit Greece and to submit proposals for the reorganization of the school. In a visit which lasted six months he considered all the circumstances with typical care and enthusiasm, and his suggestions are incorporated in a comprehensive report. His proposals will be generally approved, and, although most of them entail considerable financial outlay and the breaking down of many barriers, it should not be beyond the genius of the Greek people to put them into effect. The Public Health Division of the Economic Co-operation Administration Mission to Greece gave enthusiastic support to all the recommendations, and a committee appointed by the Greek Minister of Social Welfare has unanimously endorsed them in principle. The school should play a vital part in solving the many problems that have arisen as a result of the trying times through which the country has passed, and it is hoped that success will attend the efforts at present being made to re-equip and re-establish the school on an even higher standard than that which it previously attained.

The London School of Hygiene and Tropical Medicine has recently welcomed to its classes the representatives of the staffs of the Greek Ministry of Social Welfare and of the School of Hygiene in Athens, and there is no doubt that all the schools of hygiene throughout Europe eagerly await the speedy return of the Athens School to its rightful place among them.

BONNIER SCOTLAND

The Department of Health for Scotland and the Scottish Health Services Council have done well to publish their reports[1] for 1951 so quickly. The Department begins its story by saying that 1951 was as a whole a static year in the health of the nation. The statistics, however, are anything but static in some directions, notably in the field of respiratory tuberculosis, which has been for many years Scotland's special health problem. The tuberculosis death rate during the whole of the nineteen-forties never fell below 60 per 100,000 of the population, and in 1947 and 1948 it was as high as 66; but in 1951 it fell to 37, compared with 47 in 1950 and 60 in 1949. Notifications have not fallen so greatly, and indeed were higher in 1951 (7,875) than during the war: but it is believed that this is largely accounted for by earlier diagnosis. Nevertheless the outlook is much better than it was, and the Department states that there are grounds for believing that the peak of incidence is passing. Another favourable trend is that of infant mortality, which was 37 per thousand live births in 1951—the lowest figure yet recorded—and although the incidence of some infectious diseases, especially whooping-cough, was higher, they caused fewer deaths among

1 *Reports of the Department of Health for Scotland and the Scottish Health Services Council, 1951*, H.M.S.O., Edinburgh.

pre-school and school-age children. One serious disappointment was a reduction of 3,000 in the number of houses built in 1951 compared with the number built in the two previous years. Scotland's need for new houses is one of the most urgent of her health problems.

Much of both reports is occupied with National Health Service matters. In Scotland the Service employs 5,200 doctors, divided almost exactly equally between the hospital and local authority services on the one hand and general practice on the other. The efficiency of the general-practitioner service is attested by the fewness of the complaints to medical service committees—only 30 last year, and in only 10 of these was the doctor found at fault. As the report says:

> When it is taken into account that the Service is used by all but a small minority of people in Scotland these figures must be held to reflect most favourably on the service given by Scottish general practitioners.

The cost of the Service, however, is a matter of comment. The number of prescriptions dispensed was just on £21m.—an average of one prescription every quarter of the year for every man, woman, and child from the Cheviots to Shetland—and the average cost was 4s. 7d. In the hospitals the daily maintenance of a patient cost, on average, 19s. 8d., and each out-patient attendance 4s. 8d.

Bound up with the report of the Department is the report of the Scottish Health Services Council. This includes the findings of a study group which was set up to examine the increase in the number of deaths attributed to heart disease in general and to coronary artery disease in particular. Whereas 20 years ago coronary heart disease accounted for one death in a hundred in Scotland it now accounts for nearly one in ten. Allowance must be made for the increase in elderly people in the population, the fall in mortality due to other diseases, and the change in emphasis in the diagnosis in cardiovascular conditions, but there has evidently been a substantial increase in incidence in middle life, not explained by the conception of the disease as a degeneration due to ageing. The Secretary of State has brought the findings of the group to the notice of the Advisory Committee on Medical Research, and four programmes of closely related research are to be put in operation.

PULMONARY EMBOLISM

The advent of anticoagulant therapy and the development of more accurate methods of diagnosis have focused the attention of physicians and surgeons on the early diagnosis of thrombo-embolism, and it is becoming increasingly evident that venous thrombosis and pulmonary embolism are very common conditions.[1,2] In the present issue of the *Journal* Dr. D. S. Short surveys the incidence and clinical features of pulmonary embolism occurring in a general hospital. Over a period of two and a half years no less than 120 patients were found to have pulmonary embolism or infarction, pulmonary infarction being the commonest of all acute pulmonary disorders encountered. More than half the cases were discovered in the medical wards, the incidence of pulmonary infarction (2.5% of all admissions) being higher than in the surgical and obstetrical wards combined. Further analysis showed that the high incidence in the medical wards was due to the occurrence of pulmonary embolism in patients with heart disease. About one-tenth of the patients with heart disease admitted to hospital during the period of survey developed thrombo-embolic pulmonary complications, a figure which emphasizes how common and serious such complications are in patients with congestive heart failure and coronary thrombosis.[3,4]

The alarming clinical state resulting from obstruction of the pulmonary circulation by massive embolism is well known and has long overshadowed the less obvious manifestations often associated with smaller pulmonary emboli. It is now fully realized that fatal pulmonary embolism is a rare condition, whereas non-fatal pulmonary embolism and pulmonary infarction, though less startling and more difficult to diagnose, are of everyday occurrence. Since minor episodes of pulmonary infarction often herald more serious attacks, and since it is likely that anticoagulant therapy might prevent further disaster, the early diagnosis of pulmonary infarction assumes great importance. Provided the diagnosis is borne in mind, there is no difficulty in recognizing those cases in which infarction is accompanied by sudden pain in the chest and haemoptysis, and in which transient cardiac embarrassment and physical signs in the chest are apparent. However, as Dr. Short found, these easily observable features are often absent. Haemoptysis was present in less than 40% of cases, and although pain in the chest was common a pleural rub was seldom heard. Quite often small infarcts produced little more than transient syncope and dyspnoea or tightness of the chest, and physical examination in such cases was unhelpful. It is therefore clearly important to assess the value of ancillary aids in the diagnosis of pulmonary infarction. Electrocardiography shows a series of changes which superficially resemble, but are really quite distinct from, those of posterior-wall myocardial infarction,[5] but these changes are probably only found when infarction is of such a degree as to throw additional strain on the right side of the heart. Radiography probably provides the most useful aid to diagnosis. In a recent paper Dr. Short has reviewed the radiological changes in pulmonary infarction.[6] Abnormalities were found in 90% of the patients examined. The classical triangular shadow of infarction was seldom seen, but areas of consolidation, basal clouding, linear shadows, and elevation of the diaphragm were common. An important radiological shadow was one which occurred at the costophrenic angle and which might be confused with a small pleural effusion. Nevertheless, it must be realized that radiological examination may be completely negative in pulmonary infarction, and the recognition of this condition ultimately depends on bedside diagnosis.

1 Bauer, G., *Lancet*, 1946, **1**, 447.
2 Murley, R. S., *Ann. roy. Coll. Surg. Engl.*, 1950, **6**, 283.
3 White, P. D., *Amer. J. med. Sci.*, 1940, **200**, 577.
4 Eppinger, E. C., and Kennedy, J. A., *ibid.*, 1938, **195**, 104.
5 Wood, P. H., *Brit. Heart J.*, 1941, **3**, 21.
6 *Quart. J. Med.*, 1951, **20**, 233.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE PSYCHIATRIC CASE AND THE LAW—II. ADMISSION TO HOSPITAL

BY

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When a patient with mental disorder is unfit for treatment at home or in a general hospital the action to be taken will depend on his attitude to the illness and how he responds to the suggestion that he should enter a mental hospital. He may realize the need for treatment and be prepared to co-operate fully, or he may have little insight into his condition and regard the suggestion as an attack on his personal liberty. He may, on the other hand, be so confused in mind that he is unable to realize his position or to express any volition at all in the matter.

Patients who can Express Volition and are also Co-operative (Mental Treatment Act, 1930, Section 1)

Over half the patients in mental hospitals in this country are *voluntary patients* under the Mental Treatment Act of 1930, and if the patient can be persuaded to seek treatment in this way the whole matter is greatly simplified. If he is over 16 years of age all that is necessary is that he should complete a form of application to be received as a voluntary patient at a hospital at which a vacancy exists. He is then able to leave the hospital provided that he gives at least 72 hours' notice in writing of his intention to do so. The medical superintendent of the hospital is under no obligation to accept the patient, and he or one of his staff will usually wish to see the case beforehand. Except in cases where the patient is likely to change his mind or where he has in fact no real insight into his condition and only agrees with the intention of discharging himself as soon as possible, the possibility of voluntary treatment should always be considered, as it avoids the element of compulsion in the relation between patient and doctor as well as the stigma which is associated with certification in the minds of relatives.

If the patient is under 16 the application is made by the parent or guardian and must be supported by a medical recommendation given either by the usual medical attendant or by a practitioner from a list specially approved for the purpose by the Ministry of Health or by the local authority.

Patients who can Express Volition but are Uncooperative

If the patient is able to state his wishes clearly but is unwilling to accept the view that he is in need of treatment his removal to a mental hospital without his consent may be necessary in the interests of his own safety and that of others.

Urgent Cases (Lunacy Act, 1890, Sections 11, 20, and 21)

If the matter is urgent and the patient must be removed at once lest he attempt suicide, exhaust himself, or harm others, it is usually advisable to arrange his admission to an *observation ward* or part of a hospital set aside for this purpose (Lunacy Act, Section 20; National Health Service Act, Ninth Schedule). The practitioner should telephone the duly authorized officer (see Part I in last week's issue of the *Journal*, page 754). If after seeing the patient the D.A.O. considers that his condition justifies removal to an observation ward he will make arrangements for admission on a "three-day order." If the patient is without relatives, or if it can be considered that he is not properly cared for, he can be brought before a justice of the peace, who may sign an order which will allow him to remain in the observation ward for 14 days (Lunacy Act, 1890, Section 21, as amended by the National Health Service Act, 1946). Before doing this the D.A.O. will usually ask the practitioner for a note stating that in his opinion the patient is in need of observation to determine his soundness of mind, and is a danger to himself or to others (or some other appropriate formula). This note is not required by law, and the D.A.O. asks for it to "cover himself." There is little point in withholding it; if the practitioner has called on the D.A.O. he will have had good reason for doing so. The decision regarding admission, however, rests with this officer and not with the practitioner.

Once in the observation ward the patient will be seen by a specialist in psychological medicine, who will be able, if the patient does not recover within the initial period or a further period of 14 days permitted after he has been visited by a magistrate, to arrange for his admission to a mental hospital as a *voluntary*, *temporary*, or *certified* patient.

If facilities do not exist for the admission of urgent cases under Section 20 of the Act in this way or if it is desirable to admit the patient direct to a mental hospital, as is always the case with private patients, use is made of an *Urgency Order* (Lunacy Act, 1890, Section 11, as amended by the Mental Treatment Act, 1930, Section 17). The order must be signed by the patient's husband or wife or a near relative who has seen the patient within two days, or by the D.A.O. of the local health authority in whose area the patient is at the time. It must be supported by one medical certificate (see Part I) and by a statement of the reasons why the patient should be placed under care forthwith. The urgency order remains in force for seven days, by which time arrangements can be made, if necessary, for certification for a longer period. In practice the medical superintendent is asked in advance if he can take the case, and the medical certificate is signed by the practitioner or by a consultant if one has been called in. Forms incorporating the necessary certificates and statements on one folded sheet of paper can be obtained from a legal stationer or, usually, from the medical superintendent of the hospital. They will be carried by a consultant if one is called in. As the situation may be regarded as urgent in a large proportion of cases in which a practitioner is called upon to act, the urgency order is a convenient and frequently used method of arranging for the admission of private patients to hospital.

Cases of Gradual Onset

Most patients under certificate in public mental hospitals have either been certified at observation wards or admitted to the hospital as urgent cases and subsequently certified within the hospital, so that the practitioner has not been concerned in the final certification. When time permits, however, use is made of the *reception order on petition* (Lunacy Act, 1890, Sections 4–8). It is, in practice, used much more often in the case of private patients and when administration of the patient's property is later likely to necessitate the appointment of a receiver.

The *petition* is written on a statutory form and is made preferably by the next-of-kin of the patient. This is supported by a statement of particulars, also on a form, and

two medical certificates. The petition must be taken to a judicial authority—that is, a stipendiary magistrate or a justice of the peace specially appointed for the purpose—who must satisfy himself that the person named in the petition is of unsound mind and a proper person to be admitted to a mental hospital. If satisfied, he signs a reception order for the patient, addressed to the medical superintendent of the hospital. For patients who have been admitted to hospital under urgency orders and who are subsequently certified on petition the single certificate already given can serve as one of the two certificates required (see Part I).

Patients who Cannot Give Expression to their Wishes but have a Good Prognosis (Mental Treatment Act, 1930, Section 5)

The sections of the Mental Treatment Act dealing with *temporary treatment* were introduced with the object of avoid certification in the case of patients suffering from states of confusion in whom the outlook for early recovery is good and who are likely to agree to become voluntary patients as soon as they are able to express any wish at all. The use of this method of admission will therefore depend upon a skilled appraisal of the patient's clinical state and of the prognosis, and for this reason one of the two certificates necessary must be given by a specialist approved for the purpose.

When the confusion is merely an incident in a case of severe psychosis of long duration, temporary treatment is unsuitable, and this method of admission should be reserved for cases of confusion, delirium, or stupor, such as occur in the puerperium, in association with toxic illnesses, or after operations. The extent of its use varies in different areas, but where it is offered it is much preferred by the relatives and, retrospectively, by the patients themselves. It is not available in Scotland. The principle is an excellent one, although it places rather more responsibility on the staff of the mental hospital, who must take action at once when the patient becomes able to express his wishes clearly and must review the case after six months, with a view either to extending the period of temporary treatment or to accepting the patient voluntarily or under certificate. A patient may enter hospital in this way from an observation ward. The practitioner, however, will be concerned with temporary treatment only when it is desirable to admit the patient to a mental hospital direct from his home.

The best method is to call in a consultant, who will almost certainly be on the list of specialists approved for the purpose. The consultant will bring with him the necessary forms, which are usually printed in one folder. They consist of an application which must be filled in by the husband or wife or a relative or by a D.A.O. from the local authority area in which the patient is seen. This is supported by a recommendation to be filled in by the consultant, in which he gives the reasons for his conclusions, and an attached medical certificate, to be given, if at all possible, by the regular medical attendant. The two medical men, who may examine the patient either together or separately, then jointly sign the recommendation and give a brief statement of such particulars about the patient as are available at the time. It is essential to contact the medical superintendent of the hospital in the first instance to be sure that a vacancy exists and that he is willing to accept a temporary patient.

The provisions for admission of temporary patients have the advantage from the point of view of the general practitioner of being less formal and more professional in nature. Like those of the urgency order they can be complied with without bringing in any public official and work well within the usual framework of a consultation or domiciliary visit.

Certification by Courts of Summary Jurisdiction (Criminal Justice Act, 1948, Section 24)

When attention has been drawn to an abnormal state of mind because the patient has been brought to a police court, the court can make an order for his reception in a mental hospital, provided that it is satisfied that the patient has committed the offence with which he is charged, and that the offence is one which is normally punishable by imprisonment. Such an order has to be supported by the certificates or testimony of two medical practitioners, who must state whether in their opinion the patient is dangerous and unfit to be at large. This is a duty which may come the way of any practitioner who examines cases at the request of the police. The certification procedure does not differ from that employed in the reception order on petition.

Aged Patients

The certification of patients over 65, or of those whose mental illness is dependent on degenerative physical disease such as arteriosclerosis or renal failure, is not desirable, especially when it is clear that the patient may not live very long. Patients of this kind are usually too ill or too lacking in enterprise to be of much danger to others, apart from the episodes of confusion which often occur in the course of a general decline in their mental powers. The need for dealing with such episodes without moving the patient is recognized at most geriatric units, and many nursing-homes specializing in old people take patients who, while certifiable, have nothing to gain from certification. No special legal provision exists for patients over 65. There is no obligation to certify a patient for whom room can be found in a geriatric ward, provided that facilities exist there for dealing with episodes of disturbed behaviour if they occur. Admission to an observation ward (Lunacy Act, Section 20) may allow time for the confusion to subside, so that if admission to a mental hospital is still necessary it can be as a voluntary patient. It is to be hoped that when enough accommodation in geriatric units becomes available the certification of patients in a terminal confusion or dementia will cease to be necessary.

Escaped Patients

The relatives of a patient who has escaped from a mental hospital and has returned to them may ask how to proceed. If the patient has been away from the hospital for less than 14 days he can be retaken without a fresh order and certificates (Lunacy Act, Section 85). He can be taken back by any member of the staff of the hospital from which he has escaped or by any person whom the medical superintendent authorizes in writing. Relatives frequently first consult the police, who are often unwilling to interest themselves in the matter unless the patient has committed an offence or is likely to do so. The first thing to do is to notify the medical superintendent of the hospital; he may decide to send one or more of his staff to collect the patient, but if the distance is great and there is little time to lose, and the patient is causing difficulty, it is well to ask the D.A.O. to help. The necessary authority can be given to the D.A.O. by the medical superintendent by telegram, provided that this is later confirmed by letter, and this will enable him to hold the patient until the hospital can send an escort. If the patient's condition gives rise to anxiety he can be admitted to an observation ward by the D.A.O. on a three-day order as a "person of unsound mind wandering at large."

If 14 days have elapsed since the patient's escape he is automatically discharged by operation of the law, and if his condition justifies certification he will, of course, have to be dealt with *de novo*. The idea that a patient who escapes in Scotland is at once free in England and Wales, and vice versa, is quite erroneous, as the necessary authority to recapture can be obtained through the Commissioners of the country in which the escape occurred (Lunacy Act, Sections 86–88). When a patient appears at the house of his relatives or in the surgery and announces that he has remained outside the hospital for the necessary period it is well to make sure that he has in fact been at large for 14 clear days—the day of the escape does not count—as it is occasionally possible to obtain an order to retake him just before the full period has expired. The arrival of an

escaped patient who proves on inquiry to be a voluntary patient is not unknown; if he wishes to return to the hospital and the medical superintendent is willing to accept him he must once again sign a form of application. Sometimes when a patient has escaped it is difficult for the doctor who sees him to be sure that he is still of unsound mind. This, however, is not important, as he can be retaken, provided that his certificates are in order, and the question of his fitness for discharge can then be decided on his return to the hospital in the light of his previous history and mental state at the time.

Discharge at Request of Relatives

The relatives of a patient who has been admitted to a mental hospital may feel his certification was not justified and may try to enlist the aid of the family doctor to get the patient discharged. If the patient has been detained under a reception order on petition the relative who signed the petition may, if he has become convinced that the patient should no longer be detained, ask for him to be discharged (Lunacy Act, Section 72). The medical superintendent can, however, prevent this in the case of a really dangerous patient by certifying in writing that he is dangerous and unfit to be at large (the "barring certificate"). In many cases it will be evident to the practitioner that the relatives' request is not in the patient's best interests, and he may be able to dissuade them from asking for the discharge. Often they have been influenced by the appeals of the patient on visiting day and have made a rash promise. In other cases the relatives feel that the certification of one of their kin is a reflection on their own mental health, and with this less reasonable group there may sometimes be no alternative but to discharge the patient and let them find out for themselves how impossible it is for him to lead a normal life. It is tempting, when they finally bring the patient and ask for him to be readmitted, to point out their error, but it is not in the patient's interests to delay his readmission, and recrimination serves no purpose.

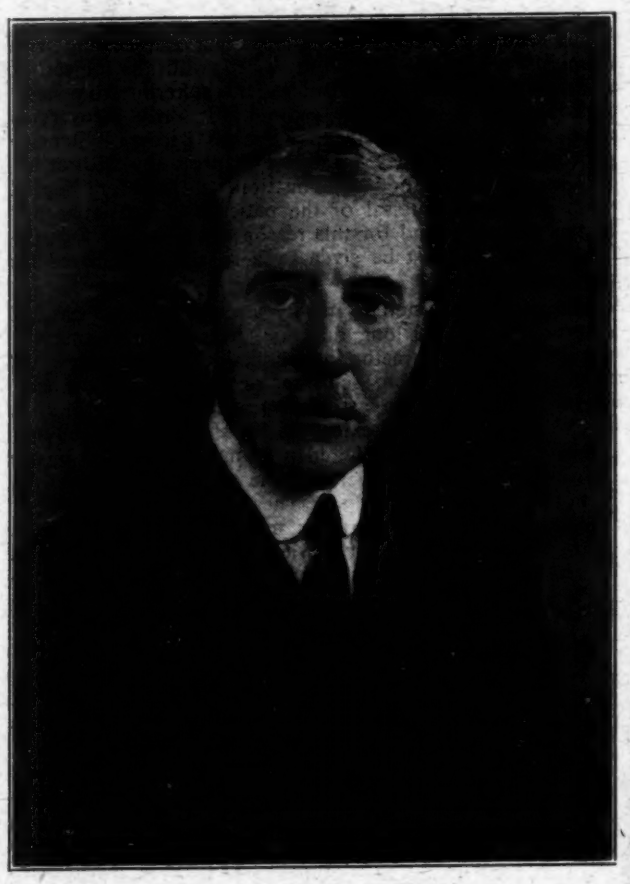
A patient may also be discharged to the care of a relative or friend (Lunacy Act, Section 79) if an undertaking is given that he will be properly cared for and prevented from doing injury to himself or others. The discharge is given by two members of the hospital management committee, who must first satisfy themselves that the relative or friend can really look after the patient. Inquiries are usually made on behalf of the committee members by a psychiatric social worker, who may ask the practitioner, if he knows the family well, for his opinion of the home circumstances. Sometimes, when a patient in a mental hospital is convalescent from a severe illness but not fully recovered and the relatives have made careful plans for his care and rehabilitation, discharge by this route is quite reasonable. Should the patient have been certified under the Criminal Justice Act (Section 24) the provisions for discharge at the request of relatives will not, of course, apply.

Next Refresher Course Article.—"Treatment of Gonorrhoea," by Dr. T. E. Osmond.

For the guidance of those interested in the formation of medical libraries in teaching and non-teaching hospitals the medical section of the Library Association compiled in 1949 a basic list of books and periodicals in the English language in steady demand and suitable for such libraries. This book list has now been revised and published under the title *Books and Periodicals for Medical Libraries in Hospitals* (Library Association, Malet Place, London, W.C.1. 16 pp. 2s.). It includes an article giving "hints on the formation of medical libraries in hospitals," which appeared in the *Lancet* (1949, **2**, 430).

MR. SAMPSON HANDLEY AT 80

On April 12 Mr. Sampson Handley celebrates his 80th birthday, and we gladly take this opportunity to offer him congratulations. In a photograph of the medical staff at the Middlesex Hospital, taken as long ago as 1905, Mr. Handley, who had then been qualified for 10 years, and was Doctor of Medicine and Master of Surgery of the University of London, appears in the background. In the front are such well-remembered Middlesex men as Douglas Powell, Henry Morris, Kingston Fowler, and Bland-Sutton. The last-named was Handley's immediate chief, whom he once described as the John Hunter of his



time. He himself carried on the Bland-Sutton tradition, with his zeal for research and his inventiveness and versatility in surgical procedures.

At about that period, the middle of the first decade of the century, Mr. Sampson Handley was just beginning his investigations in the cancer research laboratories at Middlesex. In his *Cancer of the Breast and its Operative Treatment*, first published in 1906, he expounded his theory that cancer spreads mainly by lymphatic permeation. The work was almost immediately translated into French and aroused interest amongst Continental surgeons, who declared that it opened new horizons. Much later, in his *The Genesis of Cancer*, Mr. Handley suggested that, in so far as a single constant precursor can be regarded as the essential cause of cancer, it is lymph stasis. He once said that he wished to be remembered only for those two theories—the spread of cancer by lymphatic permeation, and the role of localized lymphatic stasis in the aetiology.

But in fact he has been much more than a laboratory experimenter. He has been one of the most brilliant and original surgeons of his generation, and this was recognized in 1931 by his election to the vice-presidency of the Royal College of Surgeons. In a long series of lec-

tures and other contributions extending over one-third of a century he has shown an extraordinary fertility of ideas. As early as the beginning of the nineteen-twenties he was using diathermy, at first for inoperable cases of breast cancer, but eventually in a wider field. He was a pioneer in the implantation of radon seeds in inoperable cases of pancreatic growth. His "darn and stay-lace" method of dealing with hernias, his early advocacy of haemo-prostatectomy for unilateral adenomatous enlargement of the prostate, of cheilotomy for restoring function in crippling traumatic arthritis of the hip—these and many other procedures demonstrated his ingenious and capable hand.

At the end of his active career, in speaking of the character of Hunter in a Hunterian oration, he devoted some attention to that neglected figure, Mrs. John Hunter, minor poetess and (sometimes embarrassed) hostess, and he paid a tribute to surgeons' wives, whose domestic routine is at the mercy of an acute appendix or a perforated gastric ulcer. Mr. Sampson Handley himself has had a happy married life of more than 40 years, blessed with four sons and one daughter, and in his place of retirement on the Norfolk coast many good wishes will go out to him from such of his contemporaries as remain, from innumerable juniors, generations of Middlesex men, and from many others in the world of surgery and cancer research.

MEDICAL SEMANTICS

The Medical Section of the Library Association held a week-end conference in Liverpool from March 28 to 31. At the opening meeting at Liverpool Medical Institution Sir HENRY COHEN spoke on "The Romance of Words; an excursion into Medical Semantics."

Words were the raw material of the librarian's craft, and if their meaning was to be appreciated their source must be recognized. Sir Henry traced the sources and routes of transmission of medical tradition from Greece to Rome and thence through Italy and France to England. Many Greek terms used by Hippocrates and Herophilus persisted in their original meaning. In the second century B.C. the Alexandrian physicians brought Greek terms to Rome and these terms were latinized (περικαρδίον, pericardium; πυλωρός, pylorus); few words of early Latin origin survived to-day, and these were mainly descriptive of the genitals (penis, testis). Following the Alexandrian invasion of Rome there was little change until the publication of the *De Fabrica* (1543) introduced to anatomy many Latin terms which survive to-day, but Greek remained the basis for pathological terms. In anatomy were used words descriptive of the appearance of organs (cochlea, a snail shell; incus, an anvil; stapes, a stirrup), while disease terms were derived by pictorial analogy (sycosis from συκον, a fig; phrynoderma from φρύνη, a toad; clinical from κλίνη, a bed). Some Greek words had come from Cretan (συριγξ, a flute; σάλπιγξ, a trumpet), and the thyroid (θυρεός, a shield) took its name from the shape of the Cretan shield. Other words resembled a process or action of a disease (lupus, a wolf—a disease which eats into the flesh and leaves scars; impetigo, from impetere, to attack).

Another group of words existed which had lost their original significance because they were based on outmoded ideas—e.g., melancholia—or on conceptions since proved false by advancing knowledge. Artery (ἀήρ, air, and τηρειν, to keep) referred originally to an air duct. As late as 1607 Topsell had referred to the trachea as the "artery of the voice." Greek mythology was the source of many medical terms from early times until the twentieth century (aphrodisiac, after Aphrodite; atropine, after Atropos; hygiene, after Hygieia; venereal, after Venus).

The simpler terms for parts of the body had derived from Teutonic through Anglo-Saxon (e.g., arm, eye, foot, blood, mouth). After the Norman conquest French terms poured into the vocabulary, and for three centuries French was the official language. Some words of Italian origin were familiar (pellagra from pella agra, rough skin; mal aria, bad air; influenza, influence). A few words owed their inception to a desire on the part of physicians to cloak their ignorance of aetiology (cryptogenic, agnogenic, idiopathic) or to conceal something from the patient (ergophobia, iatrogenic). Some words were onomatopoeic in origin (belch, hiccup, borborygmi).

Medical literature was strewn with eponymous terms, named after observers (Bright's disease), locality (Malta fever), occupation (woolsorter's disease), or even victim (Thomsen's disease). Eponyms were generally unsatisfactory. They sometimes incorrectly attributed priority and gave undeserved fame (Graves's disease); they were too vague to conform to modern knowledge (e.g., Bright's disease), and occasionally the attribution of one name to several conditions had led to ambiguity (Paget's disease of bone, and of nipple; four conditions named Pick's disease).

Chance, superseded theories, ignorance, true and false analogies, have played a major part in the evolution of medical nomenclature. More recently it has fallen a victim to the modern craze for initials (P.A.S., D.D.T., Q fever).

What rules should govern the making of new words? Scholarship should not be allowed to go mad. We must not give way to the crank and ultra-purist who objects to hybrids such as appendicitis, oculogyric, and visceroptosis, but wants suimobile instead of automobile, and supertension or hyperpiesia for hypertension. We must, however, avoid if possible the violation of the principles of classical construction. A new word must indicate to the educated man the notion it is intended to convey. It must not have been previously used for a different notion (e.g., radial, in new anatomical nomenclature), and it must not lead to confusion.

LEONARDO'S QUINCENTENARY

The Royal Academy and the Science Museum are celebrating the birth of Leonardo da Vinci with an exhibition at Burlington House which includes many scientific and medical notes and drawings. The drawing, "The Child in the Womb," reproduced below, has been lent by the Queen. (See also p. 804.)

[Photo Studios, London

Reports of Societies

FATIGUE DISSECTED

A symposium on "Fatigue," arranged by the Ergonomics Research Society, was held at the College of Aeronautics, at Cranfield, near Bletchley, from March 24 to 27. About 150 people assembled, largely workers from university and industrial research laboratories, and including visitors from Scandinavia, the Netherlands, and the United States. The programme made it possible to survey the whole subject in its physiological and psychological aspects, with attention to environmental factors and methods of testing.

Earliest Signs of Fatigue

The subject was opened by Sir FREDERIC BARTLETT, Professor of Experimental Psychology, Cambridge, who began by defining fatigue as follows:

> Fatigue is a term used to cover all those changes in the expression of activity which can be traced to the continuing exercise of that activity under its normal operational conditions, and which can be shown to lead, either immediately or after some delay, to a deterioration in the expression of that activity, or, perhaps more simply, to results within the activity which are not wanted.

This definition, he said, concerned only normal operational conditions. If the operator was subject to conditions beyond the normal range for the activity concerned, such as excessive noise, vibration, great heights or depths, extreme speed or load, severe heat or cold or humidity, there were then superimposed other effects upon those of the continued exercise. It had often been shown that reports which an operator made about himself, his aches and pains, his localized or generalized malaise, his feelings of tiredness, are consistent with almost any kind of performance. It must be remembered, however, that the effects of subjective states may often be delayed. In an advanced state of fatigue the operators' reports of their unpleasant experiences become more pronounced, but they could not by themselves be regarded as constituting the criteria for which psychologists were looking. They might mark acute or chronic fatigue, but in practice the earlier stages were the more dangerous.

It was easy, Sir Frederic Bartlett continued, to construct a type of ergographic recording which would separate the successive stages of the operation involved. First of all there was the normal reaction-lag to the initiating stimulus, then the contraction phase, then the brief interval which marked the directional change-over from contraction to relaxation, and finally the relaxation phase itself. As the operation continued, irregularities in the succession began to appear, first perhaps a little prolongation of the interval before the directional change of movement took place, and closely associated with this a tendency to rush the relaxation phase. There was at this time no recordable change of output, no awareness on the part of the operator that the successive stages of the operation had been in any way affected, but, as the process went on, irregularities began to invade every phase in the succession. Contraction might be rushed or delayed, the interval of directional change lengthened or shortened, relaxation dragged out or precipitated. The earliest sign of fatigue was this increasing irregularity in the timing, and, of course, the changes were more pronounced in "paced" performance than in free activity. The electronic recording mechanism in the Nuffield Research Unit of the Psychological Laboratory at Cambridge was invaluable for detecting such irregularities. There was some evidence that mental fatigue followed the same pattern, but to record it would involve considerable improvement of technique.

"Dogged Does It"

Sir Frederic Bartlett added that advanced or acute fatigue was frequently, perhaps always, accompanied by complaints of localized discomforts. When this advanced state of fatigue arose there was very little that could be done about it except by enforcing rest or by getting the person to meet the situation with a certain dogged fortitude. When the latter was attained some extraordinary things might happen. At all of its stages the characteristics of fatigue came and went, the irregularity of timing appeared and disappeared, the display field began to break up and then reformed. In what seemed to be the final stage of near exhaustion dogged fortitude would often carry a man through to a kind of "second wind," but why it did this, and what the mechanism was, no one seemed to know.

Discomfort in Modern Life

The physiological side was opened by Professor G. P. CROWDEN, Director of the Department of Applied Physiology, London School of Hygiene and Tropical Medicine, who gave a general review of the factors influencing fatigue and subsequent recovery under the headings of work, environment, time, and personal. He drew particular attention to the fatiguing effect of static muscular effort due to bad posture which limited the essential blood supply and consequently the oxygen supplied to working muscles. In this connexion he commented on the influence of temperature and the need for operatives at work-benches to have seats of appropriate height, so that they could sit or stand without handicap to performance. He also pointed out that rush-hour travel in tube and bus was a great contributory cause of fatigue for workers in London and other large cities, particularly at the end of a day spent in doing work in which little general body movement was involved. Immobilization, the postural strain of strap-hanging, vibration and buffeting while starting and stopping, coupled with heat stress due to the proximity of fellow beings, all contributed to fatigue. It was most important that fatigue should not become cumulative from day to day, and the home environment was a major factor concerned with the recovery aspect of the problem.

Wartime Studies

A brief history of research in this field was given by Dr. R. C. BROWNE, of the Nuffield Department of Industrial Health, University of Durham. The first simple conception of muscular fatigue and its separation from mental fatigue had been advanced about 70 years ago. More complicated tests had then been developed in the early years of this century, when it came to be recognized that there was probably a diurnal performance rhythm, with fairly sizable individual differences in response to continued activity. It was also realized that fatigue might be masked by greater effort, that the sense of monotony was a type of fatigue, and that fatigue had a close relation to health.

The first world war stimulated work on the effect of sleep deprivation upon performance, and it was shown by laboratory tests that lack of sleep initially stimulated performance and then caused it to deteriorate. It was noticed also that there was very little connexion between the subjective feelings of a fatigued person and his objective achievements. War conditions also emphasized that lessening of fatigue could come about only by attention to all the physical and psychological conditions of the work, and the idea of environmental design began to develop.

The second world war made better known the signs and symptoms of fatigue in people faced with complicated situations, such as air pilots, and also widened the knowledge of the relationship between performance and environment. It was shown that very long application to a task produced symptoms in the subject and signs in the performance. Performance, moreover, was shown to be closely related to

environment and to have a natural diurnal and nocturnal rhythm. Dr. Browne suggested that in view of the many functions which the human body could carry out there could not be a single entity called fatigue, nor could it be subject only to a single test.

A Physiologist's Analysis

Dr. A. HEMINGWAY, of the Department of Physiology, Leeds School of Medicine, discussed the physiological background. He defined fatigue as decrement in output with continued use of a tissue or organ, the process being reversible, and recovery taking place during rest. In terms of neuromuscular activity the failure of a muscle to continue to develop tension at the original level might be due to a failure of the fibres themselves or to a failure of the nerve impulses to reach and affect the muscle fibres; the latter might be due to impairment in conduction in the fibres, at the synapses or at the muscle end-plates. It had been shown that with continuous use impairment could occur in all these situations, despite the classical view that the muscle end-plate was the seat of neuromuscular fatigue. The transmission of nerve impulses or the development of tension in muscle fibres presumably entailed a release of energy and subsequent restoration of the system responsible for its release—a process which might depend on local resynthesis or on the use of stored material. In the long run continued restoration was likely to require the arrival of fresh material and the removal of metabolites. The time of onset of fatigue at a particular rate of working might therefore be determined by the rate of transport of materials by the working tissue to or from the site of activity, and the maintenance of this store of materials over a period would depend upon its supplementation. Sometimes side-effects prevented the full use of the transport mechanism. For example, the circulatory adjustments necessary for temperature regulation during prolonged and severe muscular effort in a warm environment took a larger proportion of available cardiac output than when the effort was made in a cool environment. Again, two forms of muscular activity might be equal in metabolic cost, but one might favour venous return to the heart and the other, owing to sustained muscular contraction, hinder it.

Elderly Workers in Heavy Industry

A field study of the work and health histories of 500 men over 50 years of age, employed in two iron foundries and a coal mine, was presented by Dr. I. M. RICHARDSON, of the Department of Public Health, University of Aberdeen. The histories showed that the proportion of the men who had at some time moved to less heavy work rose steadily during the fifties and sixties to a figure of 80% in those over 70 years of age. But the ages at which these moves were made varied widely. The number of changes to less heavy work was small in the twenties and thirties. It began mainly in the forties, and in this particular sample reached a maximum in the fifties. Information about reasons for the change to less heavy work had been difficult to obtain. In about 60% of the histories the move from heavy work had been made during or following illness or injury, often of a minor nature. Health assessments, made without physical examination, showed that some three-fourths of the 500 men were in good health. The men in the sixties were, over all, a slightly less fit group than those in the fifties. Of those over 70, 95% were still fit men.

The Urge to Work

Dr. D. RUSSELL DAVIS, of the Psychological Laboratory, Cambridge, suggested that one of the influences which caused adults to work was the anticipation of psychological dangers, which were removed by the doing of the work itself. The more successfully the work was done the quicker the decrease in the anticipation of psychological danger. Much of the activity observed was anticipatory and precautionary and due to the anxiety of the subject. But if the subject was able to achieve a satisfactory standard of work his confidence increased and the danger of failure seemed to recede. At the same time he might become less alert and careful and therefore more liable in some circumstances to sustain accidents by being caught unawares. On the other hand, if he was relatively unsuccessful in his work the danger of failure might become more imminent, and the changes in his responses more frequent, rapid, and vigorous, even unrestrained, excessive, and impulsive. With these changes in activity might be associated feelings of inadequacy, dissatisfaction, and tiredness. Such changes in responses might develop within a few minutes and have serious effects on the quality of the work, especially if skilled; equally they might develop over days, weeks, and months, and be responsible for nervous disorders—for example, anxiety states. If they persisted, well-established habits might be weakened in the same way as, in the laboratory, responses became weakened when reinforcement was withheld.

In a contribution from Massachusetts Hospital, Boston, Dr. ROBERT S. SCHWAB described an ergographic study of muscular activity in a group of patients with subjective complaints of fatigue, another group with neurological disorders in which fatigue played a dominant part, and, thirdly, a group of normal controls. Neostigmine was injected intramuscularly, but only in cases of myasthenia gravis was this drug shown to be specific in its beneficial effect in altering the fatigue curve. No change in the curve was produced by the chewing of coca leaves or cocaine wax. Pure rest was found to benefit only the muscular type of fatigue.

Tropical Fatigue

Tropical fatigue in the Royal Navy was the subject of a paper by Surgeon Commander F. R. ELLIS, R.N., of the Medical Research Council's Tropical Research Unit, Singapore. He said that when healthy men served for a prolonged period in an unduly warm climate some of them suffered from tropical fatigue, evidenced by lethargy, mental retardation, reduced powers of concentration, irritability, forgetfulness, and mild changes in personality; these changes were associated with excessive sweating, unsatisfactory sleep, skin diseases, loss of weight and appetite, and vague digestive disorders. In a healthy community, however, serious breakdown would not be encountered very often, and there would be little reference to the condition in routine sickness records. Most of the adverse effects could be surmounted temporarily when it was necessary to make a special effort.

The cause of tropical fatigue, said Surgeon Commander Ellis, was generally exposure to unduly warm conditions for months or a few years, and the effects were reversible when the climatic stress was removed. When people were exposed for many years or for generations to excessively warm living and working conditions the adverse effects were more permanent, and very much less reversible, and "tropical deterioration" appeared. Further investigations were required to determine the physiological and psychological basis of these conditions as they might affect men and women who came to live in the Tropics from more temperate zones, as well as the indigenous races who had been there all the time. In the meanwhile the main cause of tropical fatigue when it occurred after relatively short exposures to excessively warm climatic conditions was abundantly clear, and the most effective remedies were, of course, improved climatic control or removal to a cooler climate.

Dr. O. G. EDHOLM, of the Division of Human Physiology in the Medical Research Council's laboratories at Hampstead, said that now that tropical disease had been largely conquered, so that in many parts of the Tropics it was reasonable to expect long and even indefinite periods of complete freedom from sickness, other problems came

forward for emphasis, especially the physical and mental deterioration which accompanied prolonged stay in the Tropics. He considered tropical fatigue as comprising physical fatigue, shown in reduced output, mental fatigue, shown by boredom, and nervous fatigue, with its emotional content and irritability. A study had been carried out by Macpherson (1948–9) on some 1,800 troops stationed in New Guinea and adjacent islands, from which it was concluded that the degree of physical deterioration found was insufficient to account for the inefficiency noted on other grounds, thereby implying that a considerable content of tropical fatigue was psychological rather than physiological. This study needed to be supplemented by studies on civilians who had voluntarily elected to adopt a career in the Tropics. The effect of moving people from the Tropics to temperate climates should also be studied. Until further work was done the limitations of life in the Tropics could not be accurately assessed.

Environmental Factors

Dr. T. BEDFORD, of the London School of Hygiene and Tropical Medicine, discussed thermal factors in the environment as influencing fatigue. The degree of fatigue experienced in industry was affected, he said, by working conditions as well as by the nature of the task. Duration of effort and environment both played their part. He reminded the Conference of the pioneer work by J. S. Haldane on the effects of high temperatures and humidity. On the basis of observations in Cornish tin mines and on laboratory experiments Haldane described the upper limit of heat at which work could be done. In 1915–18 H. M. Vernon brought forward the first scientific evidence of the influence of temperature on accident causation. Since then many studies had been made under the auspices of the Industrial Health Research Board on the influence of thermal environment on industrial output, and the adverse effects of high temperatures had been fully shown, including a raised incidence of accident and sickness. Even when industrial workers could work stripped to the waist every effort should be made to keep the wet-bulb temperature below 80° F. (26.7° C.); when clothing must be worn, still lower temperatures were needed if the work was to be done efficiently, and the wet-bulb temperature should probably not be much above 72° F. (22.2° C.).

Many interesting experiments were described in the course of the symposium. Major J. W. T. REDFEARN, R.A.M.C., mentioned a preliminary investigation carried out in the Army Operational Research Group on the effect of fatigue on finger tremor. Sleep deprivation in itself did not appear to affect tremor, neither did several hours of hard work on muscles other than those acting on the finger. But exercise of the muscles acting on the finger markedly increased tremor, especially at the low frequencies. Acute exertion sufficient to cause a marked rise in pulse rate brings about increased tremor in the middle frequencies, probably related to the release of adrenaline. Mr. W. T. SINGLETON, of the Psychological Laboratory, Cambridge, described the deterioration of performance on a short-term perceptual-motor task, showing that there can exist a kind of fatigue which does not manifest itself in the time or accuracy of movements so much as in an increasing interval between movements, a matter which has often been underestimated by motion-study engineers. From Copenhagen came an analysis of the reasons why negative or eccentric movement is less fatiguing than positive or concentric movement, and from Stockholm an analysis of different working procedures in a steel factory from a physiological point of view; from Cornell University some studies on the use of muscular potentials as indicators of effort in visual tasks; and from the Department of Human Anatomy at Oxford some observations on the relation of anatomy and fatigue. In fact, in the course of three days every aspect of the subject, from mechanics to philosophy, was threshed out, though no one quoted Samuel Butler: "Life is one long process of getting tired," which sums it all up.

Correspondence

Stage Hypnotism

SIR,—Correspondence keeps appearing in your columns and even from eminent medical pens in the daily press on what will soon be called the menace of stage hypnosis. So far, however, no doctor has published the clinical history of a single case which would enable us to judge for ourselves the severity of the danger, nor is there any indication of the frequency with which cases occur.

I have seen three of these performances in the past five years and should like to suggest that there are other aspects to the matter. Personally, I found them excellent entertainment. I enjoyed the sporting element in the contests that develop between the hypnotist and his subject, and I found the demonstrations most thought-provoking in relation to the problems of my own work. But, surely, of wider importance must be the value of these gentlemen as allies to the unfortunates among us who have to fight the Battle of the Bottle of Medicine. Of the crowds leaving the theatre after a performance I always think, "There, at least, are several hundreds who, if occasion arises, will be quicker to appreciate the relationship between mind and body."

To those with an urge to promote public safety by proscriptive measures I can suggest many other subjects, and the type of entertainment that fills the hypnotist's theatre for the other 51 weeks of the year would not be at the bottom of the list of those worthy of investigation.—I am, etc.,

London, N.W.1. J. F. TUTHILL.

Hypnotism in Medicine

SIR,—I should be glad of the opportunity to line up my findings with those of Dr. J. E. Middlemiss in his letter (March 1, p. 488) describing treatment by hypnosis of a case of asthma.

I practise as an allergist, and in the course of my work often use hypnosis in certain cases. I have found that, whereas a patient suffering from pure psychogenic asthma can be treated and often cured by hypnotherapy, the bronchitic asthmatic and the pure allergic or sensitized patient cannot derive any lasting benefit. True enough, complete relaxation can be procured in nearly all cases, so that some relief may be expected in the pure allergic case, but it will by no means amount to a cure. It is also notable, as I pointed out in a talk at a recent meeting of the International Association of Allergists, that even cases of non-allergic and non-bacterial eczema and also certain cases of angioneurotic oedema and vasomotor rhinitis may well be cured by hypnotherapy.

But, to differ from Dr. Middlemiss, I would stress that in my opinion hypnosis cannot by any means be the single method of choice in these conditions, useful as it may prove in individual cases.—I am, etc.,

Liverpool. A. E. BERNSTIEN.

Pseudocyesis

SIR,—Having read with much interest the recent correspondence on pseudocyesis, I am prompted to relate details of a case in my own practice a few years before the last war.

A lady aged about 40 years, who was unknown to me, came to the surgery one evening, accompanied by a friend, to book me for her confinement. As she appeared to be nearing full term I remonstrated with her in a kindly way for leaving it so late before making any arrangements. Taking her history, I learned that she had been married many years but this was the first pregnancy, and also that 37 weeks had elapsed since the last period. I suggested an immediate antenatal examination, which disclosed two facts: (1) The abdomen, which had the normal contour of very advanced pregnancy, was resonant on percussion, and (2) although the breasts were somewhat enlarged there were no nipple changes and no secretion.

Deciding that it was a case of pseudocyesis, I explained to the incredulous patient and her friend that a further examination at her home on the following day was essential and that a short anaesthesia would be necessary. Accordingly the next morning, in the presence of her friend, I induced a mild chloroform anaesthesia and immediately the abdomen returned to normal proportions.

The friend could scarcely believe her own eyes, and when the patient recovered consciousness two or three minutes later she instinctively looked down at her side expecting to see the newborn baby lying there. She could not be convinced that a trick had not been played on her. Later I explained the phenomenon to her, but if her friend had not been a witness I feel sure she would have been convinced that I had given her something to dissolve her eagerly awaited firstborn.

—I am, etc.,

Bournemouth. J. H. MILLER.

Penicillin Dangerous?

SIR,—May a dental surgeon be permitted to add his views on this subject? Many dental surgeons have a pernicious habit of popping a penicillin cone into every extraction socket, and this, I feel, is a principal contributory factor to the increasing number of resistant strains of organisms, quite apart from the chances of sensitizing the patient. To add to the selling power of these preparations, it is also customary for the manufacturers to spice the minimal penicillin dosages with a varied assortment of sulphonamides. It is to be hoped that the bigger and better antibiotics now becoming available will not be abused in the same way.—I am, etc.,

Liverpool. JOHN HALLAM.

Anaemia in Pregnancy

SIR,—The argument on whether there exists a physiological anaemia of pregnancy and whether pregnant women should automatically receive iron has gone on for a long time. Different authors produce with painstaking care and regularity sets of figures proving or disproving the same points, and I do not think it impolite to suggest that the conclusions reached by Drs. Nancy Benstead and G. W. Theobald (February 23, p. 407) may not represent the last word in the dispute. But does this matter? A fact beyond dispute, but which is seldom mentioned, is that we are treating women and not haemoglobin levels. The haemoglobin level is a laboratory abstraction, which, however useful, bears no constant relation to health. We must all have been many times surprised by the pallid sickly-looking patient with a constant haemoglobin level of 95 to 100%, and the ruddy, healthy-looking one with 75% or less. My point is that, while the haemoglobin level of pregnant women, in Bradford and elsewhere, may frequently be "subnormal"—whatever this means—very few of them exhibit signs or symptoms suggestive of, or attributable to, anaemia. I am sure that most practitioners will agree with me that the proportion who do is much less than the 60% said to be "subnormal" or "severely anaemic."—I am, etc.,

Theale, Berks. H. S. SAMUEL.

SIR,—The result of Drs. Nancy Benstead and G. W. Theobald's excellent paper (February 23, p. 407) will surprise only those who are complacent about the present standard of our diet. It is indeed of some concern that 6.5% of 2,000 consecutive pregnant women attending their antenatal clinic, and who were otherwise reasonably healthy and took the extra rations and vitamins supplied by the Ministry of Food, were severely anaemic at the 16th week of pregnancy, before any significant hydraemia occurred; furthermore, that 60% of all cases had subnormal values—i.e., less than 12 g. Hb in 100 ml. blood. It is a poor consolation that the corresponding figures published recently from the Chicago Lying-in Hospital were even worse—i.e., 12% and 63% respectively.

It has been found that the human foetus contains 300–400 mg., the placenta about 500 mg., iron at term[4]; this amount together represents 25–33% of the total iron stored by the mother. About 90% of this iron is drawn from the mother during the second half of pregnancy; still, there are many, as quoted by Theobald and Benstead, who consider the resulting anaemia "physiological" and due mainly to haemodilution. This controversy continues, although it has been demonstrated in large series[1] of pregnant women that no incidence of hypochromic anaemia could be found if the iron content of the daily food habitually taken before and during pregnancy exceeded 15 mg. In an excellent summary by workers in the Postgraduate Medical School it was stated recently[7] that, while several factors may influence the iron metabolism in pregnancy, the dominant one is the excessive demand of the foetus for iron in the later stages of pregnancy. If the mother has satisfactory iron reserves she might fall into a latent deficiency; in cases of poor reserves she will be precipitated into a manifest anaemia.

If 60% of all pregnant women supplied with extras from the Ministry of Food were found anaemic, it is only reasonable to suppose that other nutritional deficiencies may also be present. Are we, then, not too complacent about the adequacy of the antenatal diet as it is actually consumed? This appears especially so in the light of Warkany's experiments,[8] the significance of which I have emphasized elsewhere.[5,6]

This experimental work found some confirmation in the long-term investigation of the Harvard group of workers, who presented evidence that in their series a statistically significant relationship was found between the quality of antenatal diet on the one hand and the incidence of toxaemia of pregnancy, prematurity, stillbirth, and neonatal death on the other.[3] In his John Shields Fairbairn Lecture given to the Royal College of Obstetricians and Gynaecologists last October Eastman stressed again the importance of dietary deficiency in the causation of prematurity, stillbirth, and neonatal death.

Has the time not come to extend the investigations to other aspects of antenatal diet as it is actually consumed?—I am, etc.,

London, W.1. Z. A. LEITNER.

REFERENCES

1 Bethell, F. H. (1945). *J. Amer. med. Ass.*, **128**, 489.
2 Burke, B. S., and Kirkwood, S. B. (1950). *Amer. J. publ. Hlth*, **40**, 960.
3 Dieckmann, W. J. (1945). *J. Amer. med. Ass.*, **128**, 488.
4 —— and Swanson, W. W. (1939). *Amer. J. Obstet. Gynec.*, **38**, 523.
5 Leitner, Z. A. (1951). *British Medical Journal*, **1**, 1110.
6 —— (1951). *Brit. J. Nutrit.*, **5**, 130.
7 Ventura, S., and Klopper, A. (1951). *J. Obstet. Gynaec. Brit. Emp.*, **58**, 173.
8 Warkany, J. (1947). *Advances in Pediatrics*, **2**, 1.

SIR,—With reference to Drs. Nancy Benstead and G. W. Theobald's article (February 23, p. 407), I would like to direct your attention to the virtues of ferrous gluconate without the addition of molybdenum or other metallic elements. I am conducting a series of cases in a clinical trial to assess the therapeutic response to the iron-containing salts, and I find I am having very encouraging results with ferrous gluconate. I feel that this preliminary communication may serve a useful purpose by allowing other practitioners to utilize this opportunity of employing a relatively simple salt of iron, which is devoid of side-reactions and whose beneficial effects are maintained for at least several months.—I am, etc.,

London, W.1. DAVID HALER.

Jocasta Complex in Adoptive Mothers

SIR,—Adoption of children often leads to a happiness equal to that experienced in a natural parent-child relationship. It is, however, connected with special factors which may make an adopted child more liable to become maladjusted than a natural child and adoptive parents more prone to emotional disturbances than natural parents.[1,2] One such factor which deserves particular attention is the severity of the Jocasta complex which is not infrequently found in adoptive mothers.

The Jocasta complex is a variation of the Oedipal theme which mainly operates between mother and son. The emotional relationship of an adoptive mother to her adopted son is normally the same as that of a natural mother to her natural son, and therefore an emotional Oedipus situation exists between them even in the absence of blood relationship. But it is just the factor of absence of blood relationship which increases the danger of a break-through of unconscious incestuous tendencies. This danger is further increased if the marital relationship between the adoptive parents is disturbed, which is more often the case in adoptive

than in natural parents. Parental discord is a very important factor in the development of a pathological Oedipus situation.[4]

The clinical histories of adoptive mothers who suffer from a Jocasta complex often reveal that their marriages were unhappy and unconsummated. They are over-indulgent to their adopted sons to an excessive degree and desirous of possessing them completely for themselves. Incestuous tendencies are usually not overtly present but are sometimes disclosed during analysis with a surprising naivety. Two typical cases will be described which illustrate the Jocasta complex in adoptive mothers.

Case 1.—A 10-year-old boy was referred to this clinic because he was very restless and destructive and aggravated his mother to an extraordinary extent. He was adopted immediately after his birth. The adoptive father was impotent and a sexual pervert. The boy became the very life of the adoptive mother. She made a god of him. She sold her business only to be able to devote her life entirely to him. When he was 3 years old he fell ill, and in order to prevent him from exerting himself she bought an unusually expensive electric railway for him which permanently occupied a whole room. She watched him continuously. When he felt sick she got sick. She openly preferred her son to her husband and never went out without him. He came into her bedroom when she was dressing herself and was crazy in his demands to be kissed over and over again. He developed numerous neurotic symptoms and the adoptive mother became a nervous wreck.

Case 2.—A little boy, aged 6, was referred because he was much afraid of the possibility that his mother would desert him. He was adopted at the age of 6 weeks and knew of it. The adoptive mother despised her husband. She lived for her son and said she loved him more than her husband. She confessed that she desired to possess her son entirely for herself. But she sadly realized that the time must come when he probably would marry. Her morbid feelings were vividly expressed when she said: "And even if he should marry he will have given his sweetest love to me."

These cases classically show that child guidance often has to be family guidance. The main problem in the treatment of the referred children was the psychotherapy of their adoptive mothers. This demonstrates that the child psychiatrist frequently has to act as adult psychiatrist.—I am, etc.,

Child Guidance Clinic, Bexleyheath. E. WELLISCH.

REFERENCES

1 Addis, R. S. (1950). *Mental Health Aspects of Adoption*, National Association for Mental Health, London.
2 Judkins, B. (1948). *Amer. J. Orthopsychiat.*, 18, 257.
3 Rautman, A. L. (1949). *Ment. Hyg. N.Y.*, 33, 424.
4 Fluegel, J. C. (1921). *The Psycho-Analytic Study of the Family*. The International Psycho-Analytic Library, London.

Experiment in Peacemaking

SIR,—I have read the correspondence on this question up to date and it is clear that something really ought to be done, but facts have to be faced. Here is one—the U.S.S.R. and the group of States linked with it have left the World Health Organization, a body which undoubtedly could have done a lot on the lines suggested in Dr. R. L. Kitching's letters (December 12, 1951, p. 1337, and March 8, 1952, p. 548).

Can we in this country alone do anything, then? I think we could if, first of all, we could be sure that we ourselves, and those whom we meet, will be quite honest and open, and if we are well disposed to each other. This surely ought to be possible with medical men.

In addition to this we should be prepared with some suggestions which would make it easier to find basic agreements. Theoretically it would, I believe, be possible to do so. For instance, if both parties accept the principles of evolutionary process and progress as applied to human beings, ethical concepts could be arrived at and agreed to, and on these concepts it should be possible to build up a tolerant world society.—I am, etc.,

Loughborough. E. H. M. MILLIGAN.

SIR,—May I join Dr. Clifford Allen (March 22, p. 652) and others in congratulating Dr. R. L. Kitching on his letters suggesting an experiment in peacemaking? His suggestion is an excellent one and will, I hope, be strongly supported by our profession. I for one will be happy to co-operate in any way he may suggest.

At the same time I cannot forget for one moment that while we in Europe are not yet actually at war, in Korea the most monstrous weapons, like napalm, are being used in our name by the United Nations. I quote from a book *Korea Reporter*, by Rene Cutforth, B.B.C. special correspondent:

"In front of us a curious figure was standing, a little crouched, legs straddled, arms held out from his sides. He had no eyes, and his whole body, nearly all of which was visible through tatters of burnt rags, was covered with a hard black crust speckled with yellow pus. A Korean woman by his side began to speak, and the interpreter said, 'He has to stand, sir; he cannot sit or lie.'"

He had to stand because he was no longer covered with a skin, but with a crust like crackling. Is there any cause on earth which can justify mankind in using weapons such as this against other human beings? And what effect will such diabolical warfare have on the soldiers, your son and mine, ordered to use such weapons and witness the terrible result?

I hope I am right in believing that there are thousands of men and women who feel as I do that there is a price which is too great to be paid for our personal safety. That price is modern warfare.—I am, etc.,

Dunmow, Essex. WINIFRED M. COPPARD.

Nature Cure

SIR,—Discussions between members of the medical profession and naturopaths never seem to be profitable to one side or the other. I have heard many, and the broadcast in "Women's Hour" on January 31 was no exception. As Dr. F. M. Lehmann says in his able letter (March 22, p. 653), the result was a draw. If broadcasting time had not been given the naturopaths would have been aggrieved, so if only for this reason the broadcast was worth while.

Dr. Lehmann describes us all as, in effect, naturopaths in disguise, but that we can do everything they can do (and more) safer, better, and quicker. We both bow to the same overriding power—the *vis medicatrix naturae*—the power that was openly acclaimed by our medical brethren at the turn of the eighteenth century but has since been neglected in our preoccupation with its anatomical, physiological, and pathological mechanisms. The point at issue would, I think, have been reached more decisively and more dramatically if, instead of comparing the rationale of different treatments of pneumonia, meningitis had been chosen. Here there is no time to evoke the *vis medicatrix naturae* with diet, fasting, or cold compresses, but a short cut with antibiotics will save the patient's life.

If the philosophy and practice of Nature Cure do not allow such treatment to be given (which they do not, because the germ theory is not accepted), or if they have no equally life-saving alternative (which they have not), there must be something wrong with the tenets of naturopaths. They are to be trusted with little more than functional disease, and then only after a diagnosis, the nature of which is often beyond their resources, has been made.—I am, etc.,

London, N.2. A. C. BARTHELS.

Economics and Doctors

SIR,—All will agree with Dr. Ffrangcon Roberts that our country faces a crisis, but few can have suspected the causes he suggests. Perhaps we have been blinded by a sentimentality now quite out of date. Dr. Roberts paints a remarkable picture—England's treasure plundered by the chronic sick, old-age pensioners, infants, and children; an irresponsible horde of non-producers gobbling up the national product in great gulps of orange juice and barium meals. And the position is not improved, he says, by those of his colleagues who prolong the lives of the useless with new and more expensive treatments.

Having decided that we "cannot afford" our present luxurious health services, perhaps Dr. Roberts will explain whether we *can* afford the inevitable result of cutting them down—an increased

burden of disease. Apparently his answer is to leave minor disease untreated, and to diagnose major disease late (thus sparing the cost of treatment for the period before the patient presents), for we might as well be clear that this will certainly be the result of charging for diagnosis and treatment at the time of illness. However, accepting for the moment the peculiar logic of the economists, that people cease to be significant when they are no longer capable of producing guns, tanks, napalm bombs, and other necessities of life, one can see that Dr. Roberts's solution would be to a limited degree successful, as it is the pensioner and the victim of chronic illness who are hardest hit by any charge for treatment, and would therefore most quickly cease to have the nation's money wasted upon them.

Apart from recent limitations due to the shortage of steel and the decline in effective demand for some consumer goods, both production and production per man-hour have risen steadily since the war, and in fact the balance of payments problem was solved shortly before the initiation of the present rearmament drive, which quickly destroyed what had been achieved. Consumption, on the other hand, has fallen and continues to do so with increasing speed; not even Government statisticians can pretend that wages and salaries are rising faster than prices. Your editorial assertion to the contrary (*Journal*, March 22, p. 642) is not very convincing in the face of the everyday experience of nine-tenths of our population.

Surely the answer to the problem lies not in how much we produce but in *what* we produce. Guns are not sold for dollars, nor do they satisfy the needs of the people. When not one new hospital has been built since the war, and scarcely a penny has been invested in improvements in the structure and facilities of general practice (despite wasteful attempts to remedy this by a fantastic hypertrophy of out-patient departments), it would be better frankly to admit that expansion or even reasonable maintenance of the Health Service must collide with all-out preparation for war.—I am, etc.,

J. TUDOR-HART.

Habitual Abortion

SIR,—This correspondence has taken a curious turn with the publication of the last letter from what I might call the endocrinological, as opposed to the clinical, protagonists in the discussion. In this letter (March 15, p. 604), Drs. P. M. F. Bishop and N. A. Richards make the following statement: "Whether she (the patient) stands this better chance because of the endocrinological, psychological, or any other effect of the implant is, to our mind, beside the point." I cannot really believe that this sentence is meant to mean what it says, for this is neither scientific nor honest. Apart from the pursuit of truth for its own sake, the answer to this question is of the greatest practical importance. If the effect is largely psychogenic, then the same results may be achieved more safely, and very much more cheaply, by the implantation of inert pellets.

The very reasonable suggestion by Dr. D. C. A. Bevis (February 23, p. 440), of a series properly controlled by the parallel use of inert tablets, would seem to me to be essential before Drs. Bishop and Richards are entitled to adopt the attitude expressed in the concluding sentence of their letter. In the hands of the ordinary clinician the complexities and uncertainties of endocrinology provide a sufficiently strong temptation to the use of the hormones empirically or even with some flavour of quackery. If the leaders of thought in this field are to encourage this unscientific trend, then the next meeting of endocrinologists should include a deputation of witch-doctors from darkest Africa to assist progress in this art.—I am, etc.,

Ashton-under-Lyne, Lancs T. B. FITZGERALD.

SIR,—The letter of Drs. P. M. F. Bishop and N. A. Richards (March 15, p. 604) seems to raise many disturbing points. The statement, "Whether (the patient) stands the better chance (of bringing a pregnancy to a successful termination) because of the endocrinological, psychological, or any other effect of the implant is beside the point," is ignoring the evidence, as the whole point of the paper is that progesterone produces the improvement. As there is no significant difference between the results of my series "without adequate treatment" and their series with progesterone implants, there seems to be little point in using such expensive means as hormones, quite apart from the discomfort to the patient produced by the implantation. The whole of your correspondence on what doctors prescribe emphasizes this point.

Further, neither series was completely successful, and the problem of treatment in habitual abortion remains unsolved; it is therefore essential that further work be done on the subject. For this reason I would say, most respectfully and sincerely, that statements from acknowledged leaders of thought on the subject that there is a moral obligation to continue one form only of treatment can lead to nothing but harm. If this teaching is generally accepted we will learn little or nothing about the aetiology and treatment of habitual abortion or any other of the ills that beset men and women in these perilous times.—I am, etc.,

Manchester. D. C. A. BEVIS.

Metric System in Britain?

SIR,—For many years it has been the custom for all new drugs to be measured for dosage in terms of the metric system, and so in the course of time the proportion of commonly used drugs measured in the apothecary system will become less and less. Confusion arises in this dual system, particularly where older drugs are compared with their modern counterparts. It is well established that all syringes for injection are marked in the metric system, and the fluid dosage is always prescribed in this way. Yet older drugs are prescribed in grains for solution in c.c.s of water for injection. It would seem that the time has come for the appointment of a committee of representatives of the medical profession, the Pharmaceutical Society, and leading manufacturers to inquire into the adoption in, say, five years' time of the international system and replace entirely the apothecary system. Similarly, packages of products should be in tens or hundreds to replace the dozen and gross.

A forward date for the change-over would be welcomed by many and lead to minimal confusion.—I am, etc.,

Bristol. D. C. BODENHAM.

Salt Intake and Prickly Heat

SIR,—There have recently been a number of articles in your *Journal* on the subject of prickly heat. Reading these and other articles, it would appear that there is a considerable measure of disagreement on the subject of its treatment. Some authors put their trust in general hygiene, others in various applications to the skin, particularly of hydrarg. perchlor. 1:1,000, while others, again, recommend smearing fats on to the skin. An article by Drs. G. O. Horne and R. H. Mole (*Lancet*, 1949, 2, 279) that was reviewed by R. M. B. MacKenna (*Med. Ann.*, 1950, p. 237) suggested that the condition was related to the sodium ion, and produced evidence to the effect that the condition was mitigated, even cured, by restricting the intake of salt and increasing that of fluids. This would appear to be in total opposition to the clinical experience of Dr. M. Egerton (*British Medical Journal*, 1950, 2, 1292).

Serving in one of H.M. ships on the South Atlantic station, based in Simonstown, South Africa, I see a number of cases of this condition, especially when cruising up the West African coast. It was, and still is, my distinct impression that additional salt is highly beneficial in the cure or mitigation of the condition. In a mild case the skin lesion clears in from 24 to 48 hours; and in the more severe and pemphigoid forms much of the distress is relieved over a similar period. During our last West Coast cruise a number of ratings were given additional salt daily. This was for a period of about five weeks that was spent in Tropical waters. The incidence of prickly heat in this group during this time was compared with a similar group of men doing similar work, but not in receipt of the additional salt. The difference in incidence was marked. The figure for those taking salt was 14%, whereas in the control group it was 53%. The dosage of salt used was two tablets containing 0.85 g. NaCl thrice daily for those suffering from the condition, while the dose

used in the group under investigation was two of the same tablets daily. Unfortunately the urinary chlorides of the two groups were not investigated, but will be in a later series. During the period under review the average wet-bulb readings were 76° F. (24° C.), with a swing between 68° F. (20° C.) and 82° F. (28° C.); the dry bulb ranged between 74° F. (23° C.) and 92° F. (33° C.), with an average of 84° F. (29° C.). The average relative humidity for the same period was in the neighbourhood of 76%, the highest readings being in such places as Lagos and Freetown, where it reached 93%. The total number of men involved in this investigation was 148.

It would appear from this that salt is not only valuable from the therapeutic point of view (Egerton), but has a place in prophylaxis.—I am, etc.,

H.M.S. Bermuda. A. A. BARTHOLOMEW.

Anaesthetic Explosions

SIR,—The letter of Dr. N. C. Hypher (February 2, p. 273) prompts me to record a sequence of events which I witnessed in a nursing-home.

A nurse obtained a cylinder of oxygen in an upright stand and proceeded to test it by turning on the main valve by means of the key. As she was rather weak in the wrist the sudden vertical blast of oxygen blew off her cap and, one would imagine, removed all particles of grit and dust from the cylinder head.

She then screwed on a 0–10-litre-per-minute oxygen flowmeter and again turned on the main valve rather suddenly. There was a startling roar as a flame some three feet long emerged vertically from the top of the flowmeter (the curved metal connecting tube having become unsoldered by the heat). The flame subsided when I turned off the oxygen, the inside of the flowmeter tube was blackened, and the white bobbin was conspicuous by its absence: a charred mass remained.

I could only surmise that the rapid ascent of the bobbin had created enough heat by friction against the side of the tube to cause its ignition, the reducing valve having been left open. It would seem that flowmeter parts should be made of materials which will not burn *in oxygen*.—I am, etc.,

Birkdale. N. S. WALLS.

Herpes Ophthalmicus and Parkinson's Syndrome

SIR,—Under the influence of the medical memorandum by Dr. Gordon Strong (March 8, p. 533), may I add the following case?

A lady of 76 developed three years ago herpes ophthalmicus, on her left side. Ten days later her daughter developed chickenpox. Six months after the herpes the old lady noticed a shaking left hand. Now her left side represents a fully developed Parkinson's syndrome. There are no signs or symptoms of cerebral arteriosclerosis.

Of course, there is nothing to support the idea that the Parkinson's syndrome is due to her pre-existent herpes zoster. Coincidence? Is the herpes zoster virus to be blamed for it? Or arteriosclerosis?—I am, etc.,

London, S.W.19. E. ROMANOWSKI.

Where Do Snails Go?

SIR,—Your special correspondent in his article on medicine in Uganda (January 19, p. 158) refers to Dr. G. Nelson's schistosomiasis survey in the West Nile district, and states that no one present at the Uganda Branch annual clinical conference could explain the disappearance of snails from pools within a week in the absence of flushing.

The most likely explanation is the death of the snails as the result of the schistosome infection or some other epizootic. The lethal effect on the snail in schistosomiasis is apt to be overlooked, and a search for empty shells is advisable when snails in large numbers disappear unexpectedly. It would at least serve to rule out the possibility of mollusc destruction by predators.—I am, etc.,

Kampala, Uganda. BASIL G. T. ELMES.

Obituary

WALTER FREUDENTHAL, M.D.

The death on March 27 of Dr. Walter Freudenthal, at the age of 58, after a protracted and painful illness, will be deeply deplored by every dermatologist in this country and by many in Europe and the U.S.A.

Dr. Freudenthal studied at the universities of Geneva and Breslau, where he completed his medical course in 1920 and was immediately appointed assistant in the dermatological clinic. In 1929 he became *Privatdozent* in dermatology. In 1933 he came to England, a refugee from Nazi tyranny. Although he knew only the rudiments of conversational English, he rapidly acquired an adequate and precise vocabulary, and was soon able, under the far-seeing and sympathetic auspices of Sir Archibald Gray, to undertake the routine histopathology for the Skin Department at University College Hospital. Before long he became an unofficial teacher of his art, and there are not a few grateful clinicians now practising who owe most of their histological skill to his painstaking supervision. He was ready at all times to accede to requests for an opinion, slides reached his laboratory through the post almost daily, and it is pertinent to record that these services were all gratuitous and offered in such a considerate and unassuming spirit that even the most eminent of his colleagues never had occasion to feel belittled.

But it was in the regular discussions at the sectional meetings of the Royal Society of Medicine that the profound basis of his knowledge became prominent and was so greatly esteemed. His lantern demonstrations will not be soon forgotten—each of them a classic, deliberate, in perfect literary style, always lucid and convincing, and never once, in the writer's recollection, disputed by other authorities present. He had a phenomenal memory, and his contributions to the literature if collected would suffice to challenge the supremacy of any advanced textbook on the subject. In 1945 he was officially appointed reader in dermatological histology to the University of London. Dr. Freudenthal was a pure scientist. Entirely absorbed and devoted to his work, he showed no interest in material gain or position, but he loved good pictures and serious books, and in his social relations displayed those simple, almost childlike qualities that gain a host of friends and never make an enemy.

Our sympathies must be extended to his devoted widow, whose proficiency in the art of section-cutting and staining contributed inestimably to the success of his earlier efforts, and later on to a reputation that will not be easily excelled.—H. C. S.

C. KILLICK MILLARD, M.D., D.Sc.

A. W. writes: Dr. C. Killick Millard was appointed medical officer of health and public analyst for the City of Leicester in 1901. He soon justified the excellent credentials with which he had come, and proved himself to be an original, energetic, and effective guardian of the public health. At this time it was often said that the amount of enteric fever in a community was a good index of the sanitary condition of the locality. If this test had been applied to Leicester in 1901 the verdict would have been very unsatisfactory—indeed a challenge to the new M.O.H. Dr. Millard at once turned his attention to the water supply, to the condition of the sewers, and to the disposal of sewage.

His survey led him to press for a larger and better supply of water. He became a warm supporter of the scheme to obtain water from the Derwent Valley, and urged that the connexions be completed without delay. Many of the defective sewers in the city were taken up and reconstructed, and the method of purification of sewage was improved. Pail closets and insanitary privies were replaced by water-closets.

These sanitary measures prevented much illness and saved many lives—for example, in the 10 years prior to 1900 the average number of cases and deaths each year of enteric fever was 216 and 31 respectively. In the following 10 years the comparable figures were 62 and 11. Ten years later still the figures were 25 and 4. Enteric fever has now become one of the rarest zymotic diseases in Leicester, the unneeded wards at the isolation hospital having been converted into a laboratory.

Another index of poor sanitation is a high infant mortality. In the 10 years prior to 1900, out of every 1,000 babies born nearly 200 died within the first 12 months of life. In 1900 Leicester had the unenviable reputation of being the worst town in the country for "epidemic diarrhoea." This disease contributed very largely to the high infant mortality rate. With the intention of reducing the number of deaths from this cause Dr. Millard started an infant milk depot, and he attended there personally twice a week to give free medical advice about the feeding of infants. This depot was the precursor of infant welfares. The average infant mortality rate for the 10 years prior to 1900 was 195.4. In 1910 it was 126.4, and in 1950 29.5.

Dr. Newsholme, in his annual report to the local government board for the year 1908, draws a comparison between Leicester and Nottingham, to the detriment of the latter. He pointed out that in Leicester pail closets had been abolished, while in Nottingham they had largely been retained, and he added that the death rate from diarrhoea had fallen 30% in Leicester and increased 17% in Nottingham. Again the death rate from enteric fever had fallen 78% in Leicester compared with 43% in Nottingham. He concluded that the large number of deaths from diarrhoea and enteric occurring in Nottingham each year would cease to occur if Nottingham adopted Leicester's methods.

In the years 1902 and 1903 smallpox was introduced to Leicester on several occasions, mainly by tramps. As it was well known that vaccination had been neglected in the city repeated prophecies were made about the fate of Leicester in the shape of a terrible epidemic of smallpox, "after which there will be fewer children left to die of diarrhoea." The tramps who carried the disease associated mainly with adults, consequently there were at first very few children attacked. The most severe cases occurred among the adults. But later on the disease spread to the children, practically all unvaccinated: yet with a few exceptions the illness was of a very mild type. In the whole epidemic over 700 cases were treated, with only 25 deaths. There is no doubt that Dr. Millard controlled the epidemic in a masterly way. He depended on prompt isolation of the patient, constant surveillance of the contacts, and on persuading them to be vaccinated at all costs. But he was opposed to "mass vaccination," which he believed to be unnecessary. So far as this outbreak was concerned he proved to be correct.

All the people of Leicester who knew Dr. Millard and his work realize how greatly they are indebted to him. They sincerely appreciate all that he did to promote the health and happiness not only of the citizens of to-day but of those of to-morrow.

Dr. M. L. Millard has informed us that his father, Dr. C. Killick Millard, who was honorary secretary of the Voluntary Euthanasia Legislation Society, has left a large stock of pamphlets on the subject of voluntary euthanasia. His executors (c/o The Gilroes, Groby Road, Leicester) will be glad to forward literature to any interested medical men or women.

EDWIN BRAMWELL, M.D., F.R.C.P., F.R.C.P.Ed.

We are indebted to Professor R. J. A. Berry for the following appreciation of the late Professor Edwin Bramwell, whose death was recorded in last week's *Journal* (p. 768): It is with the very deepest regret that I have just seen—I can hardly say read, for failing eyesight no longer permits—the announcement of the death of a very old, valued, and highly esteemed friend. Surely there cannot be many more of the friends of yesteryear who are to precede me. I knew Edwin Bramwell for many years, and have long admired his work, his friendliness, and his devotion to his profession and to his and my university, which he served so truly well. Nor in my appreciation of a very dear friend must I forget his helpmeet and now, alas, widow, for she too was of the profession, not with a medical qualification, but as the daughter of a well-beloved professor of anatomy. Hence was I doubly attached to Edwin Bramwell. However few and inadequate these words may be, they are very, very sincere, for it is hard to part with a lifelong friend, especially one like Edwin Bramwell.

G. P. MILLS, F.R.C.S.

Professor T. L. Hardy writes: May I add to the obituary notice (March 22, p. 662) a tribute to the memory of Mr. Percival Mills, whose friendship my family and I enjoyed for over 30 years? His retirement, enforced by poor health, from the staff of the Birmingham General Hospital and Medical School in 1938 was a disaster, for not only was he a very able surgeon and an excellent clinical teacher, but he possessed unusual intellectual gifts and had that indefinable quality of personality which made him a ready prey to the cartoonist. Mills was a man of brilliant wit, somewhat devastating at times, though always pungent and apt. He was an excellent committee man. During argument which seemed interminable and irreconcilable he would sit quietly doodling, ultimately producing a resolution which united all points of view and satisfied all parties. His home life was ideally happy, and he shared with his able wife many interests—a love of literature and music, gardening, expeditions in search of rare plants (for both were enthusiastic botanists), long tramps together on the hills of Wales and Cumberland; and when these activities were denied him he took to the gentle art and became a skilled trout fisherman. He had a preference for the river Usk near Brecon, but he was an adept at brook fishing, and there were few places where Mills could not cast a fly. Although illness curtailed his professional activities at the height of his powers he continued to lead a useful and productive life in the country. He restored and extended an old farmhouse and surrounded it with a garden notable specially for its rock plants and roses. Here he lived the life of a country gentleman, playing an active part in local affairs. A genial host and a delightful companion, his concern was ever that his friends should enjoy themselves, and days with Christine and Percy in their Worcestershire home will be an abiding memory for many.

Mr. James Gore writes: As one of Mr. Percival Mills's house-surgeons I feel I should like to add a little colour to the admirable obituary notice in the *Journal* of March 22. Mr. Mills was a man of the greatest kindness of heart, a fact which he was often at pains to conceal from the unobservant under a somewhat crustacean exterior—though his pawky sense of humour was capable of giving amusement (upon reflection) even to his victims. Perhaps I may be permitted one example. He had just performed an operation of considerable difficulty in which he had been assisted by a senior colleague who had wished to observe his technique, and, as we started the next case, he innocently observed, "I always get on much better when I have an assistant whom I can curse." The many who were helped and encouraged by Percy Mills will greatly regret the passing of this outstanding individualist in a surgical world tending more and more to uniformity.

G. W. M. FINDLAY, C.B.E., M.D., D.Sc., F.R.C.P.

The death of Dr. G. W. M. Findlay on March 14 was recorded in the *Journal* of March 22 (p. 658). We are indebted to Dr. R. R. Willcox for the following appreciation:

The sudden and untimely death of George Marshall Findlay has come as a great personal shock to his many friends and colleagues in all parts of the world. His ebullient mind and an apparently fathomless capacity for taking on more and more work led them—alas, falsely—to believe that he would last for ever. Certainly the profession has lost an outstanding member at the very peak of his usefulness.

I first became associated with him in 1942, when, in the rank of brigadier, he was consulting physician to the West African Command. Here his many interests centred round the large research laboratory which he had fostered. At that time, before penicillin was in general supply, he was making his own crude preparation and treating yaws with it. He was a tireless worker and the fortunate possessor of a brain which on being shown a few trees could visualize the whole forest with a fair degree of accuracy. During this time he directed a mass treatment operation on the 82nd West African Division for schistosomiasis contracted a few weeks prior to sailing for Burma, and investigated a typhus epidemic in northern Nigeria. I was lucky in being associated with him in both of these ventures, in which the work in hand, visits to local hospitals, and visits to native markets were all interwoven. These days are some of the happiest of my life. Dr. Findlay, who was a non-smoker and almost a non-drinker, would exhaust many a mess by indulging in long walks in search of snails or other material immediately after a considerable plane or car journey.

The war over, he became editor of *Abstracts of World Medicine*—a task he performed with distinction. Many of his West African colleagues were employed as abstracters in the early issues. His real love, however, was research, and soon, aided by certain grants and the kindness of Professor Buttle, he established a laboratory at the School of Pharmacy, at Bloomsbury Square. Here he worked in the lunch hour and again after tea, studying the viruses of poliomyelitis, Coxsackie, and others. Recently he directed some attention to non-specific urethritis and was making some progress, employing mouse-brain and cortisone techniques. I saw him regularly during this phase. He was never downhearted when his experiments failed. Such temporary reverses made him the more optimistic. Not content with this double job, he continued writing as prodigiously as he had done for years. Apart from his many papers on many subjects, including the treatment of tropical ulcer and yaws in the Gold Coast by the use of oral antibiotics, which he was directing by a sort of remote control from London, his *Recent Advances in Chemotherapy*, a monumental work rightly praised by the critics, took shape volume by volume. Much of this must have been done in the train between London and Radlett. Many felt that he had taken on too much, as perhaps he did.

My last memory of him, a common one in recent years, was sitting at his desk in B.M.A. House with papers piled to the ceiling and books and manuscripts strewn all over the floor. However busy, he was always pleased to help, encourage initiative, and to take on more work. If a man was ever killed by overwork, surely this was such a case.

MICHAEL HESELTINE, C.B.

N.L.T. writes: On reading the notices both in the *British Medical Journal* (March 13, p. 663, and March 29, p. 716) and in the national press following the death of Mr. Michael Heseltine, I have felt that they have done less than justice to one striking characteristic—his unfailing courtesy and helpfulness to those who had the misfortune to appear before the General Medical Council in its disciplinary capacity and those whose duty it was to represent them. If there was anything at all that he could do to assist in these cases he invariably did it, and on a number of occasions I found that he had foreseen matters of difficulty or embarrassment and was ready with suggestions before any approach had been made to him at all. Many others who had occasion to meet him over this aspect of his duties have indicated that they share my own lasting appreciation of this one of his many qualities.

Dr. JAMES DUNLOP, who died recently, was the son of the stationmaster at Baillieston, and was a teacher before taking up medicine as a career. He graduated M.B., Ch.B. at the University of Glasgow in 1910, and was in general practice in the east end of Glasgow for 25 years. He held strong political views, and for some years he was a member of the Glasgow Corporation and a magistrate. In 1937 he entered the Glasgow public health service. Dr. Dunlop was a member of the Scottish subcommittee of the old Insurance Acts Committee of the British Medical Association in 1921–2, and was a member of the Medico-Political Committee in 1933–4. He also represented his constituency at the Annual Representative Meetings in 1932, 1933, 1934, and 1935. In recognition of his services as medical officer for civil defence in Glasgow he was appointed O.B.E. in 1943. Until quite recently he was working as a ship surgeon, travelling to and from the Far East.

Sir Alexander S. M. Macgregor, formerly medical officer of health for Glasgow, writes: Will you allow me to contribute an appreciation of the late Dr. James Dunlop, as we came to be warm friends when he was a member of the public health staff of Glasgow Corporation? His most outstanding service to the community was during the war as medical officer in direct charge of the casualty service of civil defence in Glasgow, a service on which he imprinted his own vigorous and forceful personality. He was chosen for this post as much for his personal qualities as for his high administrative abilities, his capacity to organize and to make decisions, and to rise superior to people and to circumstances. This service, under his guidance, rapidly developed until there were in the city some 76 first-aid posts and ambulance depots. He became at once the moving spirit in these enterprises. Because of his attractive and kindly personality and unfailing sense of humour he was able to arouse the enthusiasm of his large staff. His ideal always was the creation of an efficient service based on a happy staff giving of their best. He was instrumental in raising quite large sums of money to provide well-equipped ambulances to replace the rather indifferent Government vehicles, and to provide amenities for the various units under his control. Indeed, every unit had its own social activities, thus preserving keenness and morale by inculcating the club spirit. Dr. Dunlop's high spirits and well-stocked mind attracted to him innumerable friends in every walk of life—among his patients in the east end of the city, where he spent most of his life as a general practitioner; among his fellow members of Glasgow Corporation, of which he was at one time a member; among his colleagues of the public health staff, as well as in political circles. He may be said to have belonged to the humanistic tradition of medicine. When he retired shortly after the end of the war his health gave rise to anxiety, and he finally contracted abroad the long illness from which he died. His loss is keenly felt by his innumerable friends, among whom I was happy to be one.

Dr. JOSEPH GASTON, who died in Nottingham General Hospital on February 6 at the age of 51, was born at Drunfin, Ballymena, Northern Ireland, on August 26, 1900, and was educated at Queen's University, Belfast, where he graduated M.B., B.Ch. in 1923. After serving in the Royal Navy from 1924 to 1926 he practised for a year at Sutton-in-Ashfield and then moved to Huthwaite, Nottinghamshire, where he took over the practice of the late Dr. R. Irvine. He married Mary, eldest daughter of Dr. Irvine, in 1931. When war broke out in 1939 Dr. Gaston carried on his

practice single-handed and took on additional work by becoming medical officer to all the local Army camps. At the time of his death he was the medical officer to a division of the St. John Ambulance Brigade. Before the war he was a keen golfer and won many trophies. He is survived by Mrs. Gaston and one son, a medical student at Clare College, Cambridge, and four younger daughters.

Dr. F. BULLOUGH, who died at his home at Hindley, near Wigan, on March 4, was born at Bolton on July 13, 1876. One of his younger brothers, Dr. W. A. Bullough, was until fairly recently county medical officer for Essex. From Manchester Grammar School, Fred Bullough won a Gaskell scholarship to Owens College, Manchester, graduating M.B., Ch.B. in 1903. After a period as an assistant in general practice and then as a ship surgeon he settled in Hindley, where he quickly built up a practice and gained the confidence and affection of the community, particularly of the poorer members. He was indeed a friend of the poor, and no nobler title could he have wished for. Dr. Bullough was a trustee and a devoted member of the Wesleyan Methodist Church. He was a golfer of the assiduous kind, and in his youth was a very good left-hand bowler at cricket. A busy industrial practice to a man who would not spare himself took the inevitable physical toll, and about eight years ago he had an attack of coronary thrombosis, from which, however, he made a remarkable recovery. He eventually resumed full practice, but at a lower pressure. He had one or two later attacks and retired from practice about three years ago, being succeeded by his partner, Dr. James Holme. Dr. Bullough's married life was ideally happy. Of his two sons, the elder, Mr. A. S. Bullough, is a surgeon in Manchester, and his daughter, also a medical graduate, is the wife of Dr. N. J. de V. Mather, the Manchester psychiatrist. At the funeral service at Hindley on March 8 the esteem, respect, and love in which Dr. Bullough was held by all were clearly demonstrated.

Dr. F. W. TAYLOR, well known as a radiologist in Blackburn and district, died peacefully in his sleep during the night of March 9. His was a life of great service and happiness. Frederick William Taylor was born in 1871, and was educated at the University of Edinburgh, where he graduated M.B., C.M. in 1894, after having had a distinguished academic career. He proceeded M.D. in 1911. While at Edinburgh he was greatly stimulated and influenced by the teaching of the late Sir Byrom Bramwell, who remained his idol and whose name was frequently on his lips. After graduation Dr. Taylor settled in Blackburn and soon built up a large general practice. His enthusiasm, thoroughness, and skill brought quick success, and he was appointed honorary assistant physician to the Blackburn Royal Infirmary in 1903 and full physician two years later. He had been greatly interested in the development of radiology for some time, and in 1914 he equipped his own private *x*-ray suite with the most modern apparatus then obtainable. In 1919 he gave up general practice and was appointed honorary radiologist to the infirmary, and thenceforward gave his whole life to medicine and to radiology. Dr. Taylor was a magistrate, and for some years was a town councillor. He had held the offices of president of the North of England Branch of the old Röntgen Society, president of the Blackburn and District Medical Society, and chairman of the Blackburn Division of the B.M.A. In 1946, after a strenuous life of 75 years, he retired to his country home and to his garden, which he loved. The following year the board of management of Blackburn Royal Infirmary dedicated to him the newly equipped *x*-ray department which, as the Taylor Department, carries a plaque in recognition of his long and distinguished service. He leaves a widow, a married daughter, and two sons, the elder of whom is also a consultant physician.

Mr. Walter Briggs writes: To one who knew Dr. Taylor intimately for almost 50 years and who lived and worked in close fellowship with him for most of that time it is difficult to avoid words of extravagance. His ability, his wide experience and knowledge, and his supreme professional and personal integrity made him a highly valued consultant. His eagerness and enthusiasm and his love to share his knowledge made him a delightful colleague and teacher. But there was more to him than that. He had a great kindliness of heart and a true charm, he was incapable of an unkind word or an envious thought, and those who knew him loved him and trusted him.

Medico-Legal

DAMAGES AGAINST STAGE HYPNOTIST

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

In December, 1948, Miss Diana Rains-Bath, then aged 19, went to the "first house" at the Brighton Hippodrome, where she saw an exhibition of hypnotism by Ralph Slater. After seeing the performance she decided to go to the "second house," and when Mr. Slater invited members of the audience to go up on the stage she went, as did some 18 others.

Slater told them it would be perfectly harmless. He told them to sit calmly, clasp their hands above their heads, and concentrate on him, when they would gradually feel sleepier and sleepier. He then chose Miss Rains-Bath and two others, and taking them to the front of the stage began to demonstrate on her, telling her that she would do exactly what he told her. She began to do so, and was clearly in a hypnotic state, but when he left her for a moment and went to the other two she began to come round. Slater then ran back to her, put both hands on her neck, moved her head forward, and in a very commanding voice told her to sleep. She relapsed into a hypnotic state.

Slater then told her that her chair was gradually getting hotter and hotter till she could sit on it no longer, whereupon she jumped up from it. Then he said: "You are going to feel like a little baby, and you will want your mother and will cry badly." Miss Rains-Bath began to cry bitterly and shouted, "Mummy, Mummy, Mummy!" at the top of her voice. Later Slater told her she was going to wake up and would shout the word "peanuts" when she sat down in the audience. She did so.

For a week or so afterwards she felt normal, but then started to suffer from periodic bouts of severe depression, which started by her waking up feeling very frightened. In the autumn of 1949 these bouts had become so serious that her parents consulted a number of doctors. In March, 1950, Dr. Sydney James Van Pelt began to treat her by gentle medical hypnosis, and by July, 1950, she was cured.

Miss Rains-Bath brought an action for damages for negligence and assault against Slater, which was tried recently[1] at Lewes Assizes before Mr. Justice Croom-Johnson and a jury. Her case was that her illness was caused by Slater, and that, as he had said that to be hypnotized by him was perfectly harmless, he was under a duty not to hurt her.

Slater's case was that he had hypnotized on the stage no fewer than 25,000 without complaint, and that nothing he had done had caused the illness. He had never assaulted her by forcibly handling her neck. He suggested that the action was part of a campaign by Dr. Van Pelt against stage hypnotism.

In his evidence Dr. Van Pelt said that he thought mass hypnotism could not be practised without danger, and certainly should not be exhibited as entertainment on the stage. He thought that to tell a girl in a trance that she was frightened and would cry for her mother would cause deep harm unless the suggestion was completely removed when she came out of the trance. The suggestion with crying was like sowing a seed which could grow into a shoot and eventually into a tree. He said that a Bill to prevent stage hypnotism was to be introduced into Parliament. Asked by Slater if he had ever made a mistaken

[1] *The Times*, March 27, 1952.

diagnosis in the whole of his career, Dr. Van Pelt replied, "In my field of mental illness—to my knowledge, no."

Mr. Justice Croom-Johnson, summing up, said that the questions for the jury were whether Slater as a professional hypnotist was guilty of negligence in treating Miss Rains-Bath and whether by touching her neck he had committed what in law amounted to an assault on her. The practice of hypnotism was perfectly lawful by the law of England, and there was no charge against Slater of being a charlatan or a humbug. The jury were asked to accept that the young woman having had things implanted in her subconscious was sick in mind for a long time. If they were satisfied that Slater told her there was no risk, they might also come to the conclusion that she did not consent to the things which were done which involved risk. So far as assault went, in law it simply meant the laying of hands by one person without a weapon upon a second person without that person's consent. Before damages could be awarded it must be proved beyond a shadow of doubt that Slater had been negligent, and the jury were not expected to swallow everything Dr. Van Pelt had said, simply because he had studied hypnotism for 15 years.

The jury, after an absence of one hour, awarded £1,000 damages for negligence, £25 damages for assault, and £107 special damages for loss of earnings, travelling, and medical expenses.

Medical Notes in Parliament

Visiting Children in Hospital

On March 26 Brigadier O. L. PRIOR-PALMER raised the question of visiting in children's wards in hospitals. He said that a number of hospitals had experimented over a long period with daily visiting in children's wards, but the majority of hospitals had not done this. Where there had been 100% success the rule had been that the mothers must be kept fully occupied during the time they were visiting. A doctor should be there at visiting hours and a sister in charge of the children's ward must have authority to prohibit visits from any parent she thought undesirable. This experiment was in operation at the Great Ormond Street Hospital for Sick Children in London. He asked the Parliamentary Secretary to the Ministry of Health to recommend that the system should be at least tried as an experiment.

Dr. BARNET STROSS supported this appeal, and Miss PAT HORNSBY-SMITH accepted the arguments in favour of visiting. The Ministry did not think that the evidence that the practice spread infection or that it upset hospital routine was decisive. The British Paediatric Association said that it could find no correlation between visiting and cross-infection. There had been a wide investigation and report in the *British Medical Journal* (January 5, p. 43) in respect of the Great Ormond Street Hospital for Sick Children, where the method had been expanded to a visit every evening. That experiment had been wholly successful. The Central Health Services Council had recommended that hospitals should adopt a less rigid attitude in the matter. The Ministry was anxious that there should be no attempt to impose precise rules which must be carried out. The Ministry advised hospital authorities, under adequate safeguards, to allow parents or guardians to visit children with reasonable frequency. Some relaxation had been allowed in several hospitals. It was advisable that hospitals which still prohibited this method should take advice and guidance from those which had tried it. The Ministry proposed to follow up its advice of two and a half years ago by calling on hospital authorities to furnish a report to the Ministry on what steps they were taking, what methods they were using, and to what extent they implemented the recommendation.

Arsenic in Cigarettes

Mr. WILLIAM SHEPHERD reported on March 27 that the arsenic content of English cigarettes had been found to range twice as high as that of American cigarettes and 25 times as high as that of Turkish and Rhodesian cigarettes. He asked whether, in view of the fact that there were grounds for the belief that this arsenic content might be the cause of the increasing incidence of cancer of the lung, steps would be taken to regulate the entry into the country of tobacco having an unnecessarily high arsenic content.

Miss HORNSBY-SMITH replied that a small-scale study showed these proportions, but the amounts were very small and varied widely in the same types of cigarettes. Mr. Crookshank was advised that arsenic in tobacco smoke was not established as a likely cause of cancer of the lung.

Cancer Publicity

Miss HORNSBY-SMITH stated on March 27 that the Central Health Services Council advised that it was undesirable at present for any cancer publicity to be carried out by any central Government organization direct to the general public. She added that Mr. Crookshank's Cancer and Radiotherapy Standing Advisory Committee was considering the merits of local schemes of cancer education.

Hygienic Bedding

Mr. HENRY STRAUSS told the House on April 1 that the orders which governed the utility scheme for bedding had been revoked, but the regulations made under the Rag, Flock, and Other Filling Materials Act, 1951, required that all fillings used for bedding should conform to the same B.S.I. standards for cleanliness as were incorporated in the utility specifications.

Adjudication Award

Mr. HILARY MARQUAND, on April 3, asked whether the negotiations on the redistribution of the central pool from which Health Service general practitioners were remunerated were actively proceeding. He asked the Minister of Health to give an assurance that no additional payments into the general practitioners' central pool would be made, following the recent adjudication, unless or until full agreement had been reached upon redistribution and other matters referred to a Working Party.

Mr. H. F. C. CROOKSHANK replied that the acceptance of the adjudicator's award was conditional on an agreement satisfactory to both sides being reached on a revised plan of distributing the central pool. Discussions were proceeding to produce a plan of distribution. He could not say when they would be concluded.

Cancer Cure

Mr. H. F. C. CROOKSHANK told Mr. PETER FREEMAN on April 3 that inquiries into the claims of Mr. Rees Evans for curing cancer had been concluded. He was considering the committee's report, but was not yet ready to make a statement.

Maternity Beds.—Hospital authorities have been advised that adverse social conditions, which include lack of help at home, justify priority, next after medical need, for admission to hospital maternity beds.

Dangerous Drugs.—The tribunal set up under the Dangerous Drugs Acts is being reconstituted.

Average Cost of Prescriptions.—The approximate average cost in England and Wales in the second half of 1948 was 2s. 8¼d. In the years 1949 and 150 it was 3s. and 3s. 2¼d. respectively. Complete figures for 1951 are not yet available, but the average cost is estimated to be 3s. 8d.

N.H.S. Payments.—On January 1, 20,859 general practitioners in Great Britain were receiving payment from the National Health Service. For the year ending March 31, 1951, the estimated total amount payable to G.P.s in Great Britain under the Health Service is £51,644,000.

Agene.—Medical Research Council investigations into the use of agene are unlikely to be completed before the end of the year.

Universities and Colleges

UNIVERSITY OF OXFORD

In a Convocation to be held on June 25 it will be proposed to confer the honorary degree of D.Litt. on William Somerset Maugham, M.R.C.S., L.R.C.P.

UNIVERSITY OF CAMBRIDGE

In Congregation on March 22 the following degrees were conferred:

M.CHIR.—W. Waugh.

M.B., B.CHIR.—M. P. Wand (by proxy), G. B. Davison.

UNIVERSITY OF GLASGOW

On March 25 the degree of M.D. was conferred *in absentia* by diploma upon N. McE. Lamont.

UNIVERSITY OF DUBLIN

The Board of Trinity College, Dublin, has appointed Professor S. P. Bedson, F.R.S., Professor of Bacteriology in the University of London, as John Mallet Purser Lecturer for 1952. It is hoped that the lecture will be delivered in May.

Professor W. J. E. Jessop, professor of physiology at the Royal College of Surgeons in Ireland, has been elected a member of the Senate of the University at the by-election caused by the elevation to the High Court of Senator F. G. Budd.

UNIVERSITY OF LONDON

The following have been appointed, or nominated for appointment or reappointment, as representatives of the University on the governing bodies of the institutions indicated in parentheses: Professors G. R. Cameron, F.R.S., and W. J. Hamilton (Royal Veterinary College); Professor R. V. Christie (Inter-University Council for Higher Education in the Colonies).

The title of Fellow of the University College, London, has been conferred upon Dr. R. H. D. Short, First Assistant, Department of Morbid Anatomy, University College Hospital Medical School.

UNIVERSITY OF MANCHESTER

On Founder's Day, May 21, the honorary degree of D.Sc. will be conferred on Professor Alexander von Muralt, professor of physiology in the University of Berne, for his contributions to medical and scientific research.

The following candidates have been approved at the examination indicated:

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*Part I:* D. L. Fox, J. Goldman, J. A. Krawiecki, K. Rawnsley.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examinations indicated:

PH.D.—R. C. Nairn, M.D.

FINAL M.B., CH.B.—*Part II:* Mary F. Allen, D. H. Alltree, S. J. Alltree, Audrey Beavan, Joyce V. Blackburne, Marjorie J. Bowness, Cicely G. Brenner, D. R. Cole, W. G. Cooper, R. H. Cranmer-Gordon, I. G. Currie, B. E. Dalton, Muriel Douglas, O. Dworetzki, A. Dyson, K. B. Edwards, L. M. Ellis, Elizabeth E. Evans, Shirley R. Fine, C. D. Fisher, Margaret K. Flenley, Pamela M. Frazer, D. C. French, R. W. Galloway, Elizabeth M. Grantham, C. Gregory, H. Halsall, Sylvia Hawthorne, D. Helbert, F. Hewitt, P. G. Holt, L. Horwich, Margaret M. Jameson, Nuala M. Kelly, J. H. Leavesley, Ann B. Lewin, Pamela R. Lipman, I. V. Lishman, Eleanor C. Lloyd, I. L. Loch, Ursula Loewenthal, P. F. Lynch, Kathleen T. McCurley, Joan E. McFarland, Kathleen McKee, N. McKie, G. M. Makhlouf, R. Middlefell, D. R. Morris, N. N. Nehra, R. Owen, C. R. Porteous, Pearl Ramkallop, A. Ramsden, L. H. Le Riche, Margaret J. Ringham, Cynthia R. Roberts, J. H. Roberts, J. S. Robinson, R. M. Rouse, P. J. W. Rowell, J. H. Rustage, R. T. Shepherd, R. I. Smith, S. E. J. Smith, A. Swithinbank, Mary B. Woodfield, S. J. P. Woods, Helen E. Worsley, V. Wright.

DIPLOMA IN PUBLIC HEALTH.—*Part I:* Angelika Haider.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—J. D. Bates, S. S. Chhabra, J. T. F. de Graft-Johnson, S. Kanchanagabhandh, [1] [2]H. B. Kennedy, [1]Tara H. Maniar, A. R. Moore, D. A. W. Nugent, P. G. Sitwala, A. Svasti.

DIPLOMA IN RADIOLOGY (RADIOTHERAPY).—*Part I:* R. H. Jones, R. V. Samapurnavanitya.

DIPLOMA IN RADIOLOGY (RADIODIAGNOSIS).—*Part I:* A. Ansell, G. Ansell, K. S. Bannerjee, P. K. Ganguli, R. I. Green, J. G. Kay.

[1]Recommended for Milne Medal in Tropical Medicine. [2]Recommended for Warrington Yorke Medal in Tropical Hygiene.

UNIVERSITY OF SHEFFIELD

Dr. D. M. D. Evans has been appointed part-time Honorary Demonstrator in Bacteriology.

Dr. M. W. A. Gatman, Lecturer in Medical Pathology, Dr. C. P. Mills and Dr. J. Parkin, Demonstrators in Anatomy, and Dr. Cynthia M. Scothorne, Honorary Demonstrator in Bacteriology, have resigned their appointments and the council have thanked them for their services to the University.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

FACULTY OF ANAESTHETISTS

The fourth annual general meeting of the Faculty of Anaesthetists was held at the Royal College of Surgeons of England on March 19, when 75 Fellows and Members, apart from the Board of Faculty, were present. The meeting was opened by a short address of welcome from the President of the College, Sir Cecil Wakeley.

The Dean of the Faculty, Mr. A. D. Marston, reported that the postal ballots for election to the Board of Faculty had resulted as follows: *Fellows*, Professor E. A. Pask and Dr. W. Alexander Low were re-elected, and Dr. M. D. Nosworthy was elected. *Members*, Dr. A. J. W. Beard was elected. The Dean reviewed the work of the Faculty during the past year and stressed particularly the increased postgraduate activities which had taken place. He also referred to the revised criteria for the training of consultants in the specialty.

The annual general meeting was followed by the Joseph Clover Lecture by Professor R. R. Macintosh on "Antecedents of Early Anaesthetic Apparatus." The annual dinner was held at the College in the evening, and among those present were Sir Cecil Wakeley, Sir John Charles, Chief Medical Officer, Ministry of Health, Dr. D. W. Logan, Principal of the University of London, and Dame Hilda Lloyd, President of the Royal College of Obstetricians and Gynaecologists. The toast of the Faculty was proposed by Sir Cecil Wakeley and replied to by Mr. Marston. The toast of the guests was proposed by Dr. J. H. T. Challis and replied to by Sir John Charles and Dr. Logan.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

On March 7 Eleanor B. Outon, M.B., B.Ch., was admitted, *in absentia*, a Licentiate and Member of the College.

CONJOINT BOARD OF IRELAND

The following candidates were duly admitted licentiates in medicine and midwifery on March 28, having passed the final examination in medicine, surgery, and midwifery of the Conjoint Board of Ireland: S. B. B. Boodhoo, L. B. Burke, J. H. Burns, B. J. Dolan, J. D. Drennan, B. M. Duncan, J. J. Fahey, G. M. FitzGibbon, Mary B. Gilmartin, Carmel M. Granville, Mary T. Healy, T. A. Mulligan, J. G. McCaffrey, K. A. W. Overton, E. W. O. Thomas.

The Services

Colonel E. H. Hall, O.B.E., late R.A.M.C., has been appointed Deputy Director-General Army Medical Services, War Office, and has been granted the temporary rank of Major-General.

A *Supplement* to the *London Gazette* has announced the following awards:

First and Second Clasps to the Territorial Efficiency Decoration.—Major F. L. Ker, O.B.E., T.D., R.A.M.C.

Territorial Efficiency Decoration and First Clasp.—Honorary Colonel W. C. Gunn, T.D., R.A.M.C., retired, and Major R. Rutherford, R.A.M.C.

Territorial Efficiency Decoration.—Major (Honorary Colonel) J. D. S. Cameron, C.B.E., Major (Honorary Lieutenant-Colonel) G. H. Wooler, Majors J. L. Taylor, T. S. Torrance, and W. W. G. Townsend, Honorary Majors M. H. A. Davison (retired) and J. S. M. Pollock (retired), and Captain C. D. Rigg, R.A.M.C.

The Queen has approved the reappointment of the following officers as Honorary Physicians and Honorary Surgeon, who held similar appointments under the late King George VI: *Honorary Physicians*, Surgeon Vice-Admiral Sir C. E. Greeson, K.B.E., C.B., Surgeon Rear-Admirals K. A. I. MacKenzie, C.B., F. G. Hunt, C.B., C.B.E., T. Madill, O.B.E., and Surgeon Captains M. Brown, J. H. B. Crosbie R.N., and Surgeon Captain G. McCoull, O.B.E., V.R.D., R.N.V.R. *Honorary Surgeon*, Surgeon Captain T. N. D'Arcy, C.B.E., R.N.

NAVAL MEDICAL COMPASSIONATE FUND

A meeting of the subscribers of the Naval Medical Compassionate Fund will be held at the Medical Department of the Navy, Queen Anne's Mansions, St. James's Park, London, S.W., on Thursday, April 24, at 3 p.m., to elect six directors of the fund.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending March 22 (No. 12) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	33	2	13	0		50	4	9	0	1
Dysentery	516	49	49	1	1	1,256	157	207	14	
Encephalitis, acute	8	1	1	0	2	7	2	0	0	
Enteric fever:										
Typhoid	1	0	0	0		7	0	1	0	2
Paratyphoid	6	0	2(B)	0		10	0	2(B)	0	
Food-poisoning	127	13		0		45	2		0	
Infective enteritis or diarrhoea under 2 years				6	5				15	19
Measles*	6,885	201	554	229	377	27,813	2518	428	114	85
Meningococcal infection	48	3	20	2	2	39	3	18	1	1
Ophthalmia neonatorum	54	6	7	0		34	0	8	0	
Pneumonia†	848	38	396	20	4	936	50	220	8	12
Poliomyelitis, acute:										
Paralytic	12	0	0	0		10	2	0	0	
Non-paralytic	8	1				3	0			
Puerperal fever§	266	33	14	1		65	7	11	1	
Scarlet fever	1,486	100	175	21	56	919	66	124	41	70
Tuberculosis:										
Respiratory			138	37				149	26	
Non-respiratory			29	4				21	4	
Whooping-cough	3,133	131	264	130	83	4,079	260	641	21	48

DEATHS in Great Towns	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	1	0	0	*0*	0	*0*	0	0
Dysentery	0	0		0			1		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	12		3	0	2	*14*		*1*	1	2
Influenza	35	2	17	1	1	*67*	6	*3*	0	5
Measles		0		0	1		2	*0*	0	0
Meningococcal infection		1	1				1	*1*		
Pneumonia	275	35		7	8	*304*	52		12	19
Poliomyelitis, acute	1	0			0	*0*	0			0
Scarlet fever		0		0	0		0	*0*	0	0
Tuberculosis:										
Respiratory	157	19	24	2	12	*163*	25	*30*	6	16
Non-respiratory		3	4	0	4		6	*5*	2	3
Whooping-cough	2	0	1	0	0	*5*	1	*3*	0	0
Deaths 0–1 year	240	24	28	3	23	*282*	26	*30*	17	27
Deaths (excluding stillbirths)	5,798	800	694	109	184	*5,928*	920	*719*	169	222
LIVE BIRTHS	8,345	1285	950	240	351	*6,756*	1085	*843*	234	387
STILLBIRTHS	197	29	20			*207*	35	*27*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Diphtheria at Darwen, Lancs

We are indebted to Dr. R. C. Webster, medical officer of health for Darwen, Lancashire, for the following report on the diphtheria outbreak at Darwen: Darwen is an industrial Lancashire borough, with a census population of 30,827. Diphtheria, often severe in character, was prevalent in 1938–43. In 1950 and in 1951, up to December, no case had been notified. A high proportion of the child population has been immunized. In 1941–3 an intensive campaign was carried out, and some 3,000 children were immunized by the medical officer of health; since then a steady maintenance programme has been continued by private practitioners and the public health clinics.

The present outbreak is mild and no deaths have occurred. The infecting strain is mitis. The outbreak began on December 3, 1951. In December, 15 cases were notified; in January, 1952, there were 7; in February, 21; in March, 32: that is, 75 in all so far. The original case was probably a boy, aged 5, who developed a palatal paresis in January. He had a history of "tonsillitis" six weeks before, and was undoubtedly a missed case. The earlier cases can be linked with this boy, and from these cases wider spread has occurred. Although school contact has played an important part, other contacts between infected households have also been important.

Cases known not to have been immunized number 48; the claims of the remaining 27 are being further investigated. Even if all these claims are correct the difference in incidence is at first sight striking, and becomes much more so when it is remembered that at least 80% of the children are immunized. For true comparison the figure of cases in the non-immunized should be multiplied by four, and it then appears that the ratio of incidence in the non-immunized to incidence in the immunized is roughly as 7 to 1. In the *Ministry of Health Bulletin* for March, 1952, Dr. W. P. D. Logan, chief medical statistician, gives the crude (i.e., non-weighted) ratio of incidence as three times as high in the non-immunized in England and Wales for 1945–7.

There is reason to suspect that not all the notified cases are true diphtheria in the strictly clinical sense. Swabbing of contacts causes notification of adults and children who may have no clinical signs—or only an indefinite sore throat—and these are notified on positive culture. Since the outbreak began there has been a sharp increase in the previous steady trickle of candidates for immunization, and many of these are for booster doses. If, as experience so far suggests, immunization continues to be protective, it seems fair to assume that this outbreak will peter out when it exhausts the supply of non-immunes. The terminal phases may be a little prolonged, because some cases may occur in the immunized and some of the immune who are in truth contact carriers will be notified as cases.

Smallpox Notifications

We went to press before the notifications in the week ending April 5 were known, but it is expected that they will number 5 in Rochdale C.B. and 1 in Chadderton U.D. The situation at Aldershot, where 1 case was reported earlier, is believed to be well under control.

Infectious Diseases

Infectious diseases in England and Wales during the week ending March 22 were less prevalent; notifications of measles decreased by 236, dysentery by 126, acute pneumonia by 102, and scarlet fever by 60. The exception to the general trend was an increase of 47 in the notifications of whooping-cough.

The largest falls in the number of notifications of measles were Middlesex 142 and Lincolnshire 91, and the largest

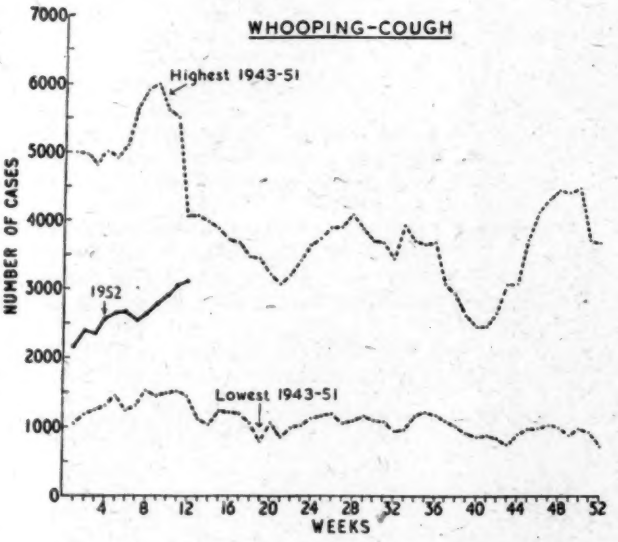
rise was Warwickshire 87. Only small variations occurred in the local returns of scarlet fever; the largest was a fall of 42 in Lancashire. Although the incidence of whooping-cough rose slightly, the largest of the local variations were falls—Durham 42 and Yorkshire West Riding 41. The notifications of diphtheria were 20 fewer than in the preceding week, a lower incidence being recorded throughout the country, though a further 6 cases were notified from the outbreak in Lancashire, Darwen M.B.

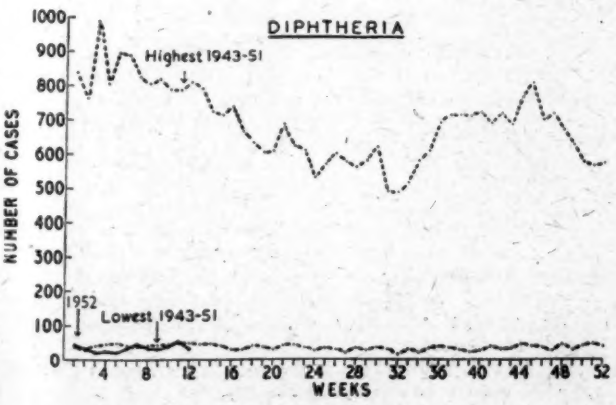
The number of notifications of acute poliomyelitis was 1 fewer for both paralytic and non-paralytic cases than in the previous week. The counties with more than one notification were Somerset 5 (Yeovil R.D. 3); Yorkshire West Riding 3; Buckinghamshire 2 (Aylesbury R.D. 2).

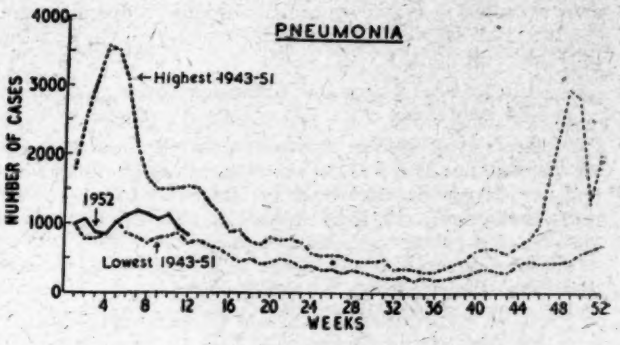
Most of the centres of dysentery showed a fall in incidence. In Lancashire the number of notifications were 50 fewer than in the preceding week. The only exception to a declining incidence was a rise of 32 in Middlesex. The largest returns during the week were: Lancashire 117 (Oldham C.B. 30, Manchester C.B. 13, Farnworth M.B. 12); Middlesex 79 (Enfield U.D. 38, Edmonton M.B. 10); London 49; Norfolk 31 (Norwich C.B. 24); Northumberland 23 (Newburn U.D. 11).

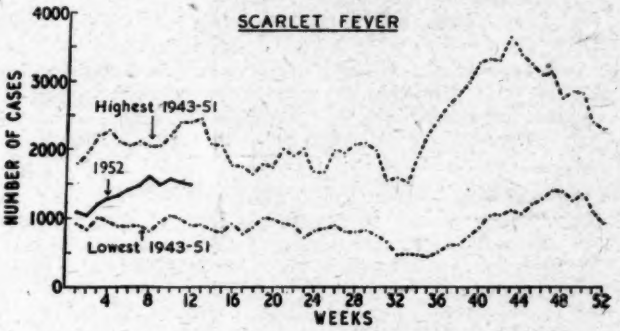
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus ---------, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in February was 115, compared with 130 (revised figure) in the previous month and 147 (revised figure) for February, 1951 (*Ministry of Labour Gazette*, March, 1952).

The following cases of industrial diseases were reported: lead poisoning 1, anthrax 1, epitheliomatous ulceration 11, chrome ulceration 17; total, 30. No deaths from industrial diseases were reported.

Medical News

Assistant Editor of B.M.J.—The job of Assistant Editor of the *B.M.J.* is advertised at page 19 of the advertisement pages. Members of the medical profession who have literary ability or journalistic experience are invited to apply. Knowledge of medicine and interest in professional affairs are as necessary as ability to write clearly. The closing date for applications is May 10.

Supply of Radium.—In future N.H.S. hospitals will not have to pay for the hire of any radium they use, but only the cost of its return by rail to Amersham. The hiring charge will in all cases be paid directly by the Ministry of Health to the Ministry of Supply, whose radiochemical centre will do all repairs other than simple straightening, and will send an inspector to examine once every five years all radium appliances in use in hospitals. Charges for radon seeds will still be met directly by hospitals, however.

X-ray Mirror for Dental Fluoroscopy.—The Ministry of Health draws attention to the potential dangers in using an *x*-ray mirror for fluoroscopic dental examination which is on sale in this country. The Ministry is advised that this instrument is potentially hazardous to the operator, the assistant, and the patient.

Bicentenary.—William Cheselden, who died on April 10, 1752, was one of the greatest operative surgeons of the eighteenth century. His most important contributions to surgery were in the field of lithotomy. He first advocated the suprapubic operation, but later abandoned it for lateral lithotomy, which became the standard method for more

than a century. He developed an iridotomy operation for cataract, and his skill as an ophthalmic surgeon is recalled by Pope's oft-quoted lines:

"I'll do what Mead and Cheselden advise
To keep these limbs and to preserve these eyes."

Cheselden's contributions to anatomy included his *Anatomy of the Human Body*, 1713, which ran through 13 editions and was the standard textbook for English medical schools, and *Osteographia*, 1733, illustrated by Van der Gucht and considered the finest osteological atlas of the century. Most of his professional life was spent at St. Thomas's Hospital, and John Hunter was his most famous pupil.

North of England Obstetrical and Gynaecological Society.—A meeting of the society was held in the Institute of Pathology, Leeds, on Friday, March 28. Professor A. M. Claye described a case of a large dermoid cyst, and Dr. A. A. Smith read a note on fertility following caesarean section. Dr. D. C. A. Bevis read a paper on the mechanism of production of kernicterus, and Mr. D. W. Currie showed a film of combined operation of colporrhaphy and fascial sling.

Homes for Unmarried Mothers.—The Fellowship of St. Michael and All Angels runs a home in South London for unmarried educated mothers. The home was founded in 1903, and is affiliated to the Church of England Moral Welfare Council. Girls from any part of the country and of any denomination are eligible. The fees are £3 3s. a week, and patients stay six weeks after the birth of the baby, but spend 10 days of this time (for the actual delivery) in a local hospital. Eighteen mothers can be accommodated. No girl leaves the home unless she has work to go to and future plans for the baby are assured. Information may be obtained from the organizing secretary, 5, Bloomfield Terrace, London, S.W.1. The home is affiliated to the National Council for the Unmarried Mother and Her Child. The *Thirty-first Report*, just issued, contains a full list of affiliated and associated homes.

Emergency Bed Service: Applications and Admissions.—During the seven days ending April 3 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,052, of whom 88.97% were admitted.

COMING EVENTS

Friends of Vellore Concert.—A Beethoven-Tchaikovsky concert will be given by the London Philharmonic Orchestra under Sir Adrian Boult at the Albert Hall on April 17, at 7.30 p.m., in aid of the Vellore Christian Medical College. Tickets (2s. 6d., 3s. 6d., 5s., 7s. 6d., 10s. 6d., and 12s. 6d.) may be obtained from the Albert Hall or from the Friends of Vellore, Annandale, North End Road, N.W.11.

Seminar on World Health.—The fourth seminar on the work of the World Health Organization will be held in Geneva during the World Health Assembly from May 5 to 17 at the Palais des Nations. Full details may be obtained from the World Federation of United Nations Associations, Education Commission, Unesco House, 19, Avenue Kléber, Paris, 16e.

International Congress of Radiology.—Arrangements are being made for the 7th International Congress of Radiology to be held in Copenhagen from July 19 to 25, 1953. It would be appreciated if as many potential members as possible would enrol well in advance. The address of the secretary of the congress is Oster Voldgade, 10, Copenhagen K, Denmark.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, April 15

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5 p.m., "*Genetics in Ophthalmology*," by Mr. Arnold Sorsby.

Wednesday, April 16

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5.30 p.m., "*Visual Fields*," by Mr. Howard Reed.

Thursday, April 17

EDINBURGH UNIVERSITY, University New Buildings, Teviot Place.—At Anatomy Theatre, 5 p.m., "*The Case for Wide Resection in Cancer Surgery*," Honyman Gillespie Lecture by Mr. Maurice Ewing.

EPSOM AND SUTTON INTER-HOSPITAL PSYCHIATRIC ASSOCIATION.—At The Manor Hospital, Epsom, 5.30 p.m., clinical meeting. Papers: "*Psychological Techniques in the Differential Diagnosis of Brain Damage*," by Drs. A. D. B. Clarke and A. M. Clarke; "*Cognitive Changes in High Grade Defectives*," by Dr. A. D. B. Clarke; "*The Manor Practice*," by Dr. J. F. MacMahon. A discussion will follow.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8, Hunter Street, Brunswick Square, W.C., 8.30 p.m., "*Impressions—Do They Last?*" by Lady Jefferson.

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Edgware General Hospital, 3 p.m., general meeting. Demonstration of cases. Papers: "*Food Poisoning*," by Dr. E. D. Hoare; "*Congenital Abnormalities of the Eye in Premature Babies*," by Mr. H. H. Skeoch.

ST. ANDREWS UNIVERSITY.—At Materia Medica Department, Medical School, Small's Wynd, Dundee, 5 p.m., "*The Diagnosis and Treatment of Arterial Disease in the Lower Extremities*," by Professor A. M. Boyd.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—5 p.m., lecture-demonstration in neurology by Dr. J. H. Paterson.

WEST END HOSPITAL FOR NERVOUS DISEASES.—At 48, Cosway Street, Marylebone Road, London, N.W., 5.30 p.m., "*Anxiety Conditions During Pregnancy*," by Dr. G. W. B. James.

Friday, April 18

BIOCHEMICAL SOCIETY.—At Liverpool University, 11 a.m., 307th meeting. Scientific papers will be read.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., 2.15 p.m., Radiodiagnosis Section Meeting. "*The Lateral Position in Chest Tomography*," by Dr. George Simon; "*Carcinoma of the Middle Lobe Bronchus*," by Dr. G. Brian Locke.

KENT AND CANTERBURY HOSPITAL, Canterbury.—8 p.m., clinical meeting.

Saturday, April 19

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Kent and Sussex Hospital, Tunbridge Wells, 10.30 for 11 a.m., "*Bronchoscopy under General Anaesthesia*," by Mr. J. V. Clark and Dr. G. P. Goodwin.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—*Assistant Psychiatrist (S.H.M.O.) at Ipswich Child Guidance Clinic*, G. Crosse, M.B., B.S., D.P.M. *Senior Registrar in Psychiatry at Norwich Mental Hospitals*, L. N. Cook, M.B., Ch.B. *Senior Registrar in Gynaecology and Obstetrics at United Norwich Hospitals*, E. M. Southern, M.R.C.S., L.R.C.P., D.(Obst.)R.C.O.G., M.R.C.O.G. *Medical Registrar at Ipswich Sanatorium*, J. M. Workman, B.M., B.Ch.

MONKS, P. J. W., M.B., B.S., F.R.C.S., Surgical Registrar to Bristol Clinical Area, South-Western Regional Hospital Board.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Ablett.—On March 24, 1952, in Leeds, to Thurza, wife of Dr. John J. L. Ablett, a son.

Jones.—On March 6, 1952, to Betty, wife of H. Glyn Jones, M.B.E., M.R.C.S., L.R.C.P., D.M.R., of Holly Bowers, Chislehurst, Kent, a son—Alan Glyn.

Mitchell.—On March 29, 1952, to Elizabeth (Dr. McKenzie Newton), wife of John Mitchell, M.D., M.R.C.P., of 146, Chorley New Road, Bolton, Lancs, a daughter.

Reid.—On April 2, 1952, at Rotunda Hospital, Dublin, to Patricia, wife of Dr. Alistair Reid, a daughter.

MARRIAGES

Fox—Wilson.—On February 1, 1952, at Umtali, Southern Rhodesia, Percy Francis Fox to Helen Rosemary Wilson, M.B., B.S., D.P.H.

Mansel-Jones—Davies.—On April 2, 1952, at Wood Green Welsh Church, London, N., David Mansel-Jones, M.B., B.S., to Mair A. Davies.

Raftery—MacHale.—On April 2, 1952, at Manchester, John Pearse Raftery, M.B., B.Ch., B.A.O., Royal Infirmary, Preston, to Julia MacHale, S.R.N., Royal Infirmary, Manchester.

Swales—Vles.—On March 14, 1952, at the British Embassy, Kabul, Afghanistan K. A. Swales, M.B., Ch.B., to Lionelle Vles.

DEATHS

Boyde.—On March 29, 1952, at his home, Harry Caine Boyde, M.B., B.S., aged 48.

Gleave.—On March 31, 1952, Humphrey Hart Gleave, M.B., M.R.C.P., of Green Acres, Bassett Avenue, Southampton.

Lowe.—On March 31, 1952, Godfrey John Ralph Lowe, M.R.C.S., L.R.C.P., of Lincoln, aged 81.

Marshall.—On April 2, 1952, at "Annisholme," Manor Park, Burley-in-Wharfedale, Yorks, Charles Robertshaw Marshall, M.D., LL.D., aged 82.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Resins for Peptic Ulcer

Q.—*Have anion exchange resins been tried in the treatment of peptic ulcer? If so, with what effect? Are there any theoretical objections to their use?*

A.—Several reports have been made of the use of anion exchange resins in the treatment of peptic ulcer—for example, M. Kraemer and D. Lehman, *Gastroenterology*, 1947, **8**, 202; F. Steigmann and R. B. Schlesinger, *Amer. J. digest. Dis.*, 1950, **17**, 361. "Amberlite IR-4" (a polyethylene polyamine substituted resin of diphenylol dimethyl methane and formaldehyde in basic form) has given satisfactory results clinically, but it does not appear to be superior to the traditional antacids from the point of view of reducing gastric acidity, and it is less effective in this respect than calcium carbonate. Doses of 2–3 g. may be given by mouth in water, and as much as 28 g. a day is not harmful. There are no theoretical objections to the use of resins, save only that they have not been proved to be effective in doses of reasonable size. Knowledge of the use of resins in the treatment of gastric disease is summarized by J. B. Kirsner, W. C. Palmer, E. Levin, and A. P. Klotz in a useful review of the whole subject of gastric antacids in *Ann. intern. Med.*, 1951, **35**, 785.

Meningeal Signs in Apical Pneumonias

Q.—*Mental confusion and signs of meningeal irritation are said to be more common in apical pneumonia than in pneumonia elsewhere in the lungs. Why is this so?*

A.—This is a difficult question. A reasonable explanation is that the symptoms are due to a stimulus referred via the cervical parietal pleura, travelling in the cervical plexus. An excess of stimuli passing up along this plexus would cause an irritable focus with spasticity and increased tonus in the extensor muscles of the neck. In the case of basal pneumonia the stimuli pass via the intercostal nerves which supply the peripheral portions of the basal parietal pleura and lead to rigidity of the abdominal muscles.

Aluminium and Silicosis

Q.—*On the one hand I have heard that aluminium dust causes disease of the lungs, and on the other hand that it prevents the development and progression of silicosis. What is the truth of these apparently conflicting statements? If aluminium dust is therapeutically useful, how is it administered?*

A.—There is no doubt that aluminium can cause pulmonary fibrosis. The clearest examples have arisen in German factories manufacturing aluminium dust for incendiary bombs during the war, where dust concentrations were extremely high (Goralewski, 1947; Baader, 1949). A diffuse pulmonary fibrosis develops with spontaneous pneumothorax as a common, and sometimes fatal, complication. A similar condition (Shaver's disease) has been reported among men exposed to bauxite fumes, which contain both aluminium and silica (Shaver and Riddell, 1947; *Sixth Saranac Symposium*, 1950). Recent animal experiments have shown that various aluminium salts can cause severe pulmonary fibrosis. The mechanism remains obscure. German workers have suggested that it is due to the denaturing of proteins by aluminium.

Silicosis is caused by free silica in the lung and is thought to be due to the action of silicic acid formed by solution of silica. If small quantities of aluminium are mixed with quartz a coating of insoluble aluminium silicate is formed over the quartz particles, and this appears to prevent or delay their fibrogenic action. The aluminium salts which cause pulmonary fibrosis are all slightly soluble. A possible explanation, therefore, for the apparent contradiction is that any combination of aluminium and silica which results in the formation of highly insoluble salts is harmless, but any combination which leaves the solubilities unimpaired may result in fibrosis. The observation that aluminium may prevent or delay fibrosis due to silica has led to the application of aluminium as a prophylactic against silicosis in a variety of forms. The argument has been extended, without theoretical justification, to the therapy of silicosis. Hitherto, the benefit reported does not appear to be greater than that which might have been achieved by simple breathing exercises and encouragement (Berry, 1948).

REFERENCES

Baader, E. W. (1949). *Z. Unfallmed. Berufskr.*, **2**, 79.
Berry, J. W. (1948). *Amer. Rev. Tuberc.*, **57**, 557.
Goralewski, G. (1947). *Z. ges. inn. Med.*, **2**, 665.
Shaver, C. G., and Riddell, A. R. (1947). *J. industr. Hyg.*, **29**, 145.
Sixth Saranac Symposium. Pneumoconiosis (1950). New York.

Glandular Regression in Hodgkin's Disease

Q.—*How useful is regression in the size of enlarged lymph nodes as a criterion of successful therapy in Hodgkin's disease?*

A.—Clinically significant remissions in Hodgkin's disease are unlikely to occur without considerable regression of enlarged lymph nodes, but similar regressions may be brought about without much clinical improvement or without arresting a downhill course. At necropsy few enlarged nodes may be found, and most of them may be densely sclerosed, with few foci of active cellular Hodgkin's disease. Apart from the shrinkage of fibrosis, the nodes sometimes show spontaneous fluctuations in size within rather narrow limits, especially in young patients. Such changes could be due to alterations in vascularity, and to variations in lymph flow while the sinuses were still patent. Less often long periods of clinical quiescence occur, unrelated to therapy, during which remarkable generalized regressions of all manifestations of disease take place. Fibrosis is not a feature of the late stages of the disease, but of the late stages of the pathological process in any site and at any stage of the disease. The evolution of this process is often rapid in some nodes in the earliest stages of the disease; on the other hand, highly cellular nodes continue to appear to the last.

Dangers from Penetrating Oils

Q.—*Do mechanics engaged in spraying cars with penetrating oils suffer from any special occupational diseases? Is there a risk of bronchial carcinoma from inhalation of the spray? If so, what precautions should be taken?*

A.—Penetrating oils consist usually of a light spindle oil to which a small amount of kerosene has been added. Sometimes in addition they contain a small percentage of colloidal graphite; occasionally fractions of 1% of such materials as cresols are added. The main use of these products, for which pressure equipment is required, is the spraying of vehicle spring assemblies. There are therefore theoretical risks of inhalation of the oil and contamination of the skin during work.

So far as can be ascertained there have been no reports of lipid pneumonia among workers engaged in this occupation. A single case of lipid pneumonia has been reported by Proudfit *et al.* (1950) in a worker who had been engaged for 17 years servicing cash-registers. He first sprayed the machines with naphtha solvent and later sprayed them with a fine liquid paraffin. The operation was carried out in an enclosed space. Extensive animal experiments to investigate the possible dangers of exposure to the inhalation of oil fogs have been carried out by Lushbaugh *et al.* (1950). Mice, rats, and rabbits were unaffected by the continuous inhalation of a fog of lubricating oil. Lipid pneumonia

did not occur under the conditions of experiment, nor were bronchial carcinomata observed. In monkeys, however, it was noted that the incidence of infectious pneumonia was greatly increased. Clearly the risks of bronchial carcinoma occurring from the inhalation of penetrating oils cannot be accurately assessed until the potential carcinogenic properties of the oil fractions used have been determined. Insufficient information is as yet available on this point.

When penetrating oils are used with pressure equipment it is suggested that the operation should not be carried out in an enclosed space, that gloves and gauntlets should be worn to protect the skin of the forearms, and that efficient cleansing agents should be supplied.

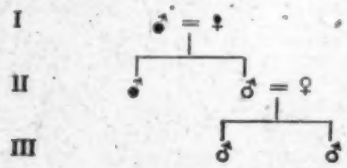
REFERENCES

Lushbaugh, C. C., Green, J. W., and Redemann, C. E. (1950). *Arch. industr. Hyg.*, 1, 237.

Proudfit, J. P., Van Ordstrand, H. S., and Miller, C. W. (1950). Ibid., 1, 105.

Inheritance of Deaf-mutism

Q.—*Two deaf-mutes married and had two sons, one of whom was also a deaf-mute, but the other was apparently normal. The latter married a healthy wife, and they had two sons, both of whom were normal.*



If one of these sons marries a normal wife is there any risk of deaf-mutism reappearing in their children?

A.—This is a very unusual history. In the majority of instances two deaf-mutes who marry have only deaf-mute offspring, as both parents are homozygous for a recessive gene. Sometimes, however, the deafness may be non-hereditary in one of the parents, and so all the children are normal. It may be that, although the deafness was non-genetic in one of the original couple, he or she was also a carrier of the gene. There is in fact some evidence that exogenous deaf-mutism is more likely to occur in a carrier. This is pointed out by the author of a recent extensive survey (Lindenov, H., *The Aetiology of Deaf Mutism.* Opera ex Domo Biol. Hered. Human. Univ. Hafniensis, vol. 8, 1945. Copenhagen). Lindenov also mentions that heredolabyrinthine disease, usually considered to be due to a dominant gene, may be severe enough to result in deaf-mutism. Possibly one of the original couple suffered from this condition, though it would then be expected that hardness of hearing would also be found in the family, and this is not mentioned in the question. Whatever the true explanation may be, however, the chance of deaf-mutism recurring in the children of the normal grandsons is very small indeed and is probably negligible. The only reservation is that marriage to a blood-relative on their father's side, or to a woman with a family history of deaf-mutism, might involve considerable risk.

Ringworm

Q.—*Where can I find information on the treatment of ringworm in children?*

A.—On p. 39 of the book "*Any Questions?*" The book can be obtained for 7s. 6d. (postage 6d.) from the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1.

Yaws and Repeated Abortion

Q.—*Is there any evidence to suggest that yaws can cause repeated abortions and miscarriage in the way that syphilis will?*

A.—No.

NOTES AND COMMENTS

Tuberculous Glands in the Neck.—Dr. P. T. K. NAYAR (Malaya) writes: In your reply ("Any Questions?" February 2, p. 285) no mention was made of the excellent results that can be obtained by the injection of ½ to 1 ml. of streptomycin solution (1 g. in 3 or 4 ml.) into the substance of the gland. Within a week the gland shrinks in size and the injection can be repeated if necessary. Sometimes enlargement returns after some months, when the same treatment can be instituted. Pus can be aspirated before the injection is given, if these glands are caseous. Similar good results have been obtained by local injection of *para*-aminosalicylic acid solution. Systemic use of these antibiotics has not been found helpful.

Mild Aperient for the Elderly.—Mr. E. W. GODDING, General Manager of the Westminster Laboratories (London), writes: In the answer under the above heading ("Any Questions?" March 1, p. 502) it is suggested that a simple anthracene-group laxative should be taken in the smallest quantity necessary, and among others syrup of senna and concentrated infusion of senna are given as suitable preparations. Your expert may not be aware that recent work (*J. Pharm. Pharmacol.*, 1950, **2**, 813) has shown that the ***B.P.*** liquid extract (with which the syrup is made) and the concentrated infusion contain only a small fraction of their expected activity with an enormous variation among different samples (in the case of the infusion a variation of eighteen times). This unsatisfactory position is due to inadequate pharmacopoeial extraction processes and instability of the active glycosides in aqueous media. Dosage with these preparations is therefore haphazard in the extreme.

OUR EXPERT writes: The paper to which Mr. Godding refers is by Fairbairn and Michaels. It has been realized for a long time that an appreciable variation in activity may be found in senna preparations. It has been found impossible, however, to introduce more exacting requirements for them into the pharmacopoeial monographs as insufficient work has so far been done on the chemistry of senna and its active constituents. The reference in your correspondent's letter to a variation of eighteen times in samples of concentrated infusion of senna hardly gives a balanced picture judged by Fairbairn's work, in which he showed that out of eight samples six varied from 0.026 to 0.076 in the percentage of glycosidal content—i.e., three times. Moreover, this work was based on an incomplete knowledge of the glycosides present in senna. Fairbairn and Saleh (*J. Pharm. Pharmacol.*, 1951, 3, 918) have shown that a third active glycoside is present and has a marked synergistic effect, increasing the total activity by about 1.7. The paper states that the factor responsible for 30 to 40% of the activity of senna is unknown. The commercial samples of liquid extract of senna and concentrated infusion of senna mentioned in the earlier paper were assayed by chemical means, but there appears to be no reference to biological assays. When there is a reliable chemical assay which has been correlated with a biological assay it may be possible to standardize the pharmacopoeial preparation. Meanwhile it must be admitted that there is some variation in activity in the official preparation, though far less than the letter from Westminster Laboratories suggests.

Is Bread Good for Diabetics?—It has been pointed out to us that the extraction rate for "national flour" is now 81% and *not* 85% as stated ("Any Questions?" March 8, p. 558). The change was effected in August, 1950 (see *Ministry of Food Bulletin*, August 12, 1950, p. 3). The present "national loaf" is made from "national flour" mixed with about 10% of imported flour of 70–72% extraction, giving a final product nutritionally equivalent to a flour of 80% extraction.

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